TREATMENT OF SEXUAL DYSFUNCTION

FIELD OF THE INVENTION

The present invention relates to methods for the treatment of sexual dysfunction and to the preparation of medicaments for the treatment of sexual dysfunction.

BACKGROUND TO THE INVENTION

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Both males and females can suffer from sexual dysfunction. Sexual dysfunctions are relatively common in the general population (see O'Donohue W, et al, *Clin. Psychol. Rev.* 1997; **17**: 537-566). The disorder may relate to seeking sexual behaviour (proceptivity) and/or to acceptance of sexual behaviour, accompanied by

15 sexual arousal (receptivity). The prevalence of sexual problems is higher in populations receiving medicaments, in particular antidepressants and antihypertensives. A need for pharmacotherapy for sexual dysfunction is increasing, but there has been very little research effort directed at finding drugs to treat sexual dysfunction.

20 Sexual dysfunctions include erectile dysfunctions of organic and psychogenic origin (Benet A.E and Melman A, 1995, *Urol. Clin. N. Amer.* **22**: 699-709) as well as hypoactive sexual desire disorders, sexual arousal disorders, anorgasmy and sexual pain disorders (Berman et al., 1999, *Urology* **54**: 385-391).

25 In males, impotence can be defined as an inability to achieve penile erection or ejaculation. Its prevalence is claimed to be between 2% and 7% of the human male population, increasing with age up to 50 years and between 18% and 80% between 55 and 80 years of age. In the USA alone, for example, it has been estimated that there are up to 10 million impotent males, with the majority suffering from problems of

30 organic rather than of psychogenic origin. Although many different drugs have been shown to induce penile erection, they were only effective after direct injection into the penis e.g. intraurethrally or intracavernosally (i.c.) and were not approved for erectile

dysfunction. US-A-5576290 discloses peptides which are stated to induce erection, but they have to be given subcutaneously e.g. by injection, and if an excessive dose is given they produce an exaggerated erectile response and stomach discomfort. Impotence treatment was revolutionized by the unexpected discovery that cGMP PDE inhibitors, e.g. pyrazolo[4,3-d]pyrimidin-7-ones were useful in the treatment of erectile dysfunction and could be administered orally, therefore obviating the disadvantages associated with i.c. administration. One such compound that is currently being manufactured is sildenafil (Viagra).

Thirty to 50% of American women complain of sexual dysfunction. Ageing, menopause, and decline in circulating oestrogen levels significantly increase the incidence of sexual complaints. In a recent publication, Berman J.R. et al. (*Int. J. Impot. Res.*, 1999, 11: S31-38), describe methodology for evaluating physiologic and subjective components of the female sexual response in the clinical setting and determine the effects of age and oestrogen status on them. Low or absent sexual drive/desire constitutes the commonest problem in the female population (Laumann et al., 1999 JAMA 281:537-544), but no therapy is available other than psychotherapy or empirical approaches. In a further publication (Bonney R.C et al., *Scrip's Complete Guide to Women's Healthcare*, PJB Publications Ltd, London, 2000) the causes and management of female sexual dysfunction are discussed, including the use of tibolone (Livial; Organon) which is a synthetic steroid that mimics the effects of oestrogen and has been reported to have mild androgenic properties, and the use of testosterone.

So far in the UK and the USA no drug has been licensed by the Department of Health specifically for the treatment of female sexual dysfunction, hence there is an unmet medical need in the treatment of female sexual dysfunction, especially sexual drive problems.

SUMMARY OF THE INVENTION

This invention is based on the realisation that substances that act as bombesin receptor antagonists have utility in the treatment of sexual dysfunction, including the behavioural component thereof, in both male and female subjects. In other words, they can provide a treatment for erectile dysfunctions of organic and psychogenic origin as well as hypoactive sexual desire disorders, sexual arousal disorders, anorgasmy and sexual pain disorders.

The invention therefore provides a method of treating sexual dysfunction which comprises administering to a subject suffering therefrom and in need of treatment an effective amount of a bombesin receptor antagonist.

The invention further provides the use of a bombesin receptor antagonist in the manufacture of a medicament for preventing or treating male sexual dysfunction or female sexual dysfunction.

Furthermore, many of the compounds of this invention have both the property of binding to bombesin receptors and the property that an effective dose can be administered orally.

BRIEF DESCRIPTION OF FIGURES

Figure 1: Effect of (S) 3-(1H-Indol-3-yl)-N-[1-(5-methoxy-pyridin-2-yl)-cyclohexyl-methyl]-2-methyl-2-[3-(4-nitro-phenyl)-ureido]-propionamide (Compound (1)) on female rat sexual proceptivity.

Figure 2: Effect of Compound (1) on female rat sexual receptivity.

Figure 3: Effect of repeated administration of Compound (1) on female rat proceptivity.

Figure 4: Effect of intracerebroventricular administration of Compound (1) on female rat sexual proceptivity.

Figure 5: Inhibitory effect of NMB on female rat sexual proceptivity and antagonism of this effect by Compound (1).

Figure 6: Results of an investigation to show whether the effect of Compound (1) on female sexual behaviour is mediated through progesterone.

Figure 7: Results of an investigation to show whether the effect of Compound (1) on female sexual behaviour is mediated through oestradiol.

Figure 8: Results of an investigation to show whether the effect of Compound (1) on female sexual behaviour is mediated through prolactin.

Figure 9: Results of an investigation to show whether the effect of Compound (1) on female sexual behaviour is mediated through LH.

Figure 10: Results of an investigation to show whether the effect of Compound (1) on female sexual behaviour is mediated through FSH.

Figure 11: Effect of Compound (1) on the sexual behaviour of normal male rats (Mount Latency).

Figure 12: Effect of Compound (1) on the sexual behaviour of normal male rats (Intromission Latency).

Figure 13: Effect of Compound (1) on the sexual behaviour of normal male rats (Number of Mounts + Intromission).

Figure 14: Effect of Compound (1) on the sexual behaviour of normal male rats (Ejaculation Latency).

Figure 15: Effect of Compound (1) on the sexual behaviour of normal male rats (Refractory Period).

Figure 16: Effect of Compound (1) on the sexual behaviour of sexually dysfunctional male rats (Mount Latency).

Figure 17: Effect of Compound (1) on the sexual behaviour of sexually dysfunctional male rats (Ejaculation Latency).

Figure 18: Effect of Compound (1) on the sexual behaviour of sexually dysfunctional male rats (% animals ejaculating).

Figure 19: Effect of (S)-3-(1H-Indol-3-yl)-N-[1-(5-methoxy-pyridin-2-yl)-cyclohexylmethyl]-2-methyl-2-[4-(4-nitro-phenyl)-oxazol-2-ylamino]-propionamide (Compound (2)) in PEG 200 on female rat sexual proceptivity.

Figure 20: Effect of Compound (2) in methylcellulose on female rat sexual proceptivity.

Figure 21: Effect of Compound (2) in PEG 200 on female rat sexual receptivity.

DESCRIPTION OF PREFERRED EMBODIMENTS

Bombesin receptors are present in hypothalamic areas. We have found that they can exert a neuromodulatory effect on sexual behaviour.

Female sexual dysfunction can be grouped into four classes (Scrip's Complete Guide to Women's Healthcare, p.194-205, 2000), which include hypoactive sexual desire disorders, sexual arousal disorders, orgasmic disorders or anorgasmy and sexual pain disorders. Hypoactive sexual desire disorders can be characterised as persistent or

recurrent lack of sexual thoughts/fantasies and lack of receptivity to sexual activity, causing personal distress. Common problems include sexual aversion disorders. Sexual arousal disorders can be characterised as persistent or recurrent inability to achieve or maintain adequate sexual excitement, causing personal distress. Common

5   problems include lack of or diminished vaginal lubrication, decreased clitoral and labial sensation, decreased clitoral and labial engorgement and lack of vaginal smooth muscle relaxation. Orgasmic disorders can be characterised as persistent or recurrent difficulty or delay in attaining orgasm after adequate sexual stimulation and arousal, causing personal distress. Sexual pain disorders can be characterised by dyspareunia,

10   (characterised by recurrent or persistent genital pain associated with sexual intercourse), vaginismus (characterised by recurrent or persistent involuntary spasm of the muscles of the outer third of the vagina which interferes with vaginal penetration, causing personal distress) and other pain disorders (characterised by recurrent or persistent genital pain induced by non coital sexual stimulation).

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The compounds of this invention are useful in the treatment of female sexual dysfunction, and this includes female sexual dysfunction associated with hypoactive sexual desire disorders, sexual arousal disorders, orgasmic disorders or anorgasmy, or sexual pain disorders.

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The psychogenic component of male sexual dysfunction has been classified by the nomenclature committee of the International Society for Impotence Research (and is illustrated in Sachs B. D., *Neuroscience and Biobehavioral Review* , 2000, **24** 541-560) as generalised type, characterised by a general unresponsiveness or primary lack of

25   sexual arousal, and ageing-related decline in sexual arousability, characterised by generalised inhibition or chronic disorders of sexual intimacy. The inventors believe that there are common mechanisms underlying the pathologies of male and female psychogenic sexual dysfunctions.

30   The compounds of this invention are useful in the treatment of male sexual dysfunction, especially drug-induced male sexual dysfunction and psychogenic male

sexual dysfunction associated with generalised unresponsiveness and ageing-related decline in sexual arousability.

We have tested compounds that are bombesin receptor antagonists using animal models that we have refined and believe are reliable and predictive, in particular with the capacity to make predictions for females. In rodents proceptive behaviour is under hormonal control, progesterone being essential for induction of proceptive behaviour in combination with oestrogen (Johnson M and Everitt B., *Essential Reproduction (3ʳᵈ edn)*, Blackwell, Oxford, 1988). The evidence for the hormonal control of proceptive behaviour in primates is conflicting, but on the whole oestrogens and/or androgens appear to enhance proceptive behaviour (Baum M.J., *J. Biosci.*, 1983; **33**:578-582). The behavioural manifestations of proceptive behaviour in the rat include "hopping and darting" movement, with rapid vibration of the ears. Tests to assess the eagerness to seek sexual contact (sexual motivation) have been reported as the most appropriate way to measure proceptivity (Meyerson B.J, Lindstrom L.H., *Acta Physiol. Scand.*, 1973; **389** (Suppl.): 1-80). Receptivity, in the rat, is demonstrated when the female assumes a lordotic position. This occurs when, on mounting, the male exerts pressure with his forepaws on the flanks of the receptive female. The main sites of neuronal control for this behaviour are the ventromedial nucleus (VMN) and the midbrain central grey area (MCG) (for review, see Wilson C.A., In: *Sexual Pharmacology*, Riley A.J. et al, (Eds), Clarendon Press, Oxford, 1993: 1-58).

Bombesin is a 14-amino acid peptide originally isolated from the skin of the European frog *Bombina bombina* (Anastasi A. et al., *Experientia*, 1971; **27**: 166). It belongs to a class of peptides which share structural homology in their C-terminal decapeptide region (Dutta A.S., *Small Peptides; Chemistry, Biology, and Clinical Studies*, Chapter 2, pp 66-82). At present, two mammalian bombesin-like peptides have been identified, the decapeptide neuromedin B (NMB) and a 23-residue amino acid, gastrin-releasing peptide (GRP).

Bombesin evokes a number of central effects through actions at a heterogeneous population of receptors. The BB_1 receptor binds neuromedin B (NMB) with higher affinity than gastrin-related peptide (GRP) and neuromedin C (NMC) and BB_2 receptors bind GRP and NMC with greater affinity than NMB. More recently evidence has emerged of two more receptor subtypes denoted BB_3 and BB_4 but due to limited pharmacology, little is known of their function at present. BB_1 and BB_2 receptors have a heterogeneous distribution within the central nervous system indicating that the endogenous ligands for these receptors may differentially modulate neurotransmission. Among other areas, BB_1 receptors are present in the ventromedial hypothalamus (Ladenheim E.E et al, *Brain Res.*, 1990; **537**: 233-240).

Bombesin-like immunoreactivity and mRNA have been detected in mammalian brain (Braun M., et al., *Life. Sci.*, 1978; **23**: 2721) (Battey J., et al., *TINS*, 1991;14:524). NMB and GRP are believed to mediate a variety of biological actions (for a review, see WO 98/07718).

The following patent applications disclose compounds capable of antagonising the effects of NMB and/or GRP at bombesin receptors: CA 2030212, EP 0309297, EP 0315367, EP 0339193, EP 0345990, EP 0402852, EP 0428700, EP 0438519, EP 0468497, EP 0559756, EP 0737691, EP 0835662, JP 07258081, UK 2231051, US 4943561, US 5019647, US 5028692, US 5047502, US 5068222, US 5084555, US 5162497, US 5244883, US 5439884, US 5620955, US 5620959, US 5650395, US 5723578, US 5750646, US 5767236, US 5877277, US 5985834, WO 88/07551, WO 89/02897, WO 89/09232, WO 90/01037, WO 90/03980, WO 91/02746, WO 91/04040, WO 91/06563, WO 92/02545, WO 92/07830, WO 92/09626, WO 92/20363, WO 92/20707, WO 93/16105, WO 94/02018, WO 94/02163, WO 94/21674, WO 95/00542, WO 96/17617, WO 96/28214, WO 97/09347, WO 98/07718, WO 00/09115, WO 00/09116. We believe that compounds disclosed in these applications can be used in the prevention or treatment of male and/or female sexual dysfunction, which is an indication that is not disclosed or suggested by the aforesaid applications, or indeed in any previous scientific publication concerning bombesin receptors.

Preferred compounds

Bombesin receptor antagonists to which this invention is applicable include both non-peptide compounds and peptide compounds. Compounds that can be formulated into compositions for oral administration, especially human oral administration, without substantial loss of activity are preferred. Many non-peptide compounds having the desired properties fall into this category.

## A) Non-peptide bombesin receptor antagonists

One preferred genus of compounds for use in the invention comprises bombesin receptor antagonists of the formula (I)

(I)
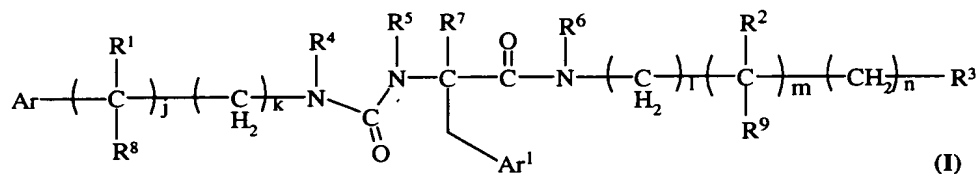
and pharmaceutically acceptable salts thereof, wherein:

- j is 0 or 1;
- k is 0 or 1;
- l is 0, 1, 2, or 3;
- m is 0 or 1;
- n is 0, 1 or 2;
- Ar is phenyl, pyridyl or pyrimidyl, each unsubstituted or substituted by from 1 to 3 substituents selected from alkyl, halogen, alkoxy, acetyl, nitro, amino, -$CH_2NR^{10}R^{11}$, cyano, -CF_3, -$NHCONH_2$, and -CO_2R^{12};
- R^1 is hydrogen or straight, branched, or cyclic alkyl of from 1 to 7 carbon atoms;
- R^8 is hydrogen or forms a ring with R^1 of from 3 to 7 carbon atoms;

- R^2 is hydrogen or straight, branched, or cyclic alkyl of from 1 to 8 carbon atoms which can also contain 1 to 2 oxygen or nitrogen atoms;

- R^9 is hydrogen or forms with R^2 a ring of from 3 to 7 carbon atoms which can contain an oxygen or nitrogen atom; or R^2 and R^9 can together be a carbonyl;

- Ar^1 can be independently selected from Ar and can also include pyridyl-N-oxide, indolyl, imidazolyl, and pyridyl;

- R^4, R^5, R^6, and R^7 are each independently selected from hydrogen and lower alkyl; R^4 can also form with R^5 a covalent link of 2 to 3 atoms which may include an oxygen or a nitrogen atom;

- R^3 can be independently selected from Ar or is hydrogen, hydroxy, $-NMe_2$, N-methyl-pyrrolyl, imidazolyl, N-methyl-imidazolyl, tetrazolyl, N-methyl-tetrazolyl, thiazolyl, $-CONR^{13}R^{14}$, alkoxy,
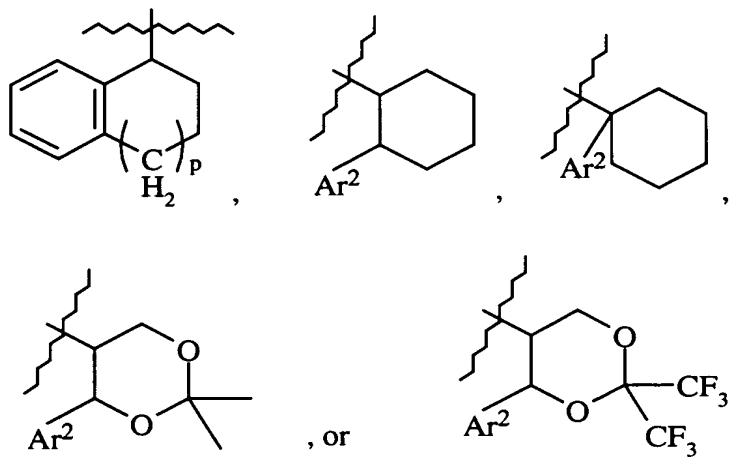
wherein p is 0, 1 or 2 and Ar^2 is phenyl or pyridyl;

- R^{10}, R^{11}, R^{12}, R^{13} and R^{14} are each independently selected from hydrogen or straight, branched, or cyclic alkyl of from 1 to 7 carbon atoms.
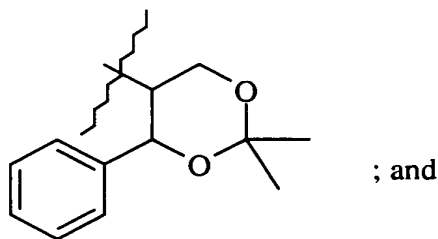
Preferred compounds are those of Formula (Ia)

(Ia)
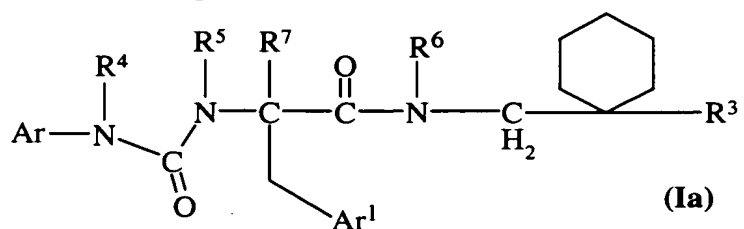
wherein

- Ar is phenyl unsubstituted or substituted with 1 or 2 substituents selected from isopropyl, halo, nitro, and cyano;

- R^4, R^5, and R^6 are hydrogen;

- R^7 is methyl or hydrogen;

- R^3 is 2-pyridyl or hydroxy; and

- Ar^1 is indolyl, pyridyl, pyridyl-N-oxide, or imidazolyl.

Other preferred compounds are those of Formula I wherein

- Ar is unsubstituted phenyl;

- R^1 is cyclopentyl or *tert*-butyl;

- R^4 and R^5 are hydrogen;

- R^7 is methyl;

- R^6 is hydrogen;

- R^3 is phenyl with two isopropyl substituents, unsubstituted phenyl, or
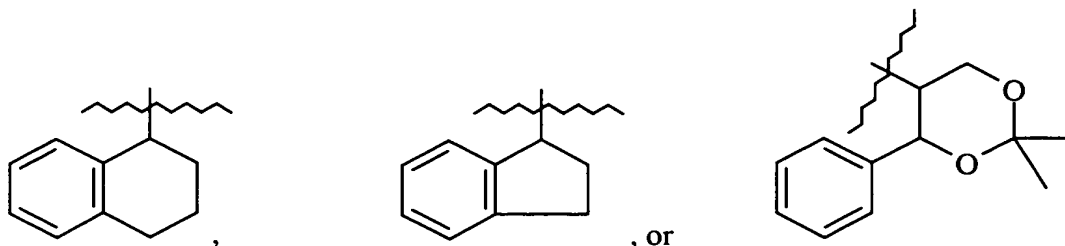

; and

Ar^1 is indolyl.

Other preferred compounds are those of Formula I wherein

- Ar is 2,6-diisopropyl-phenyl, 4-nitro-phenyl, and 4-cyano-phenyl;

- R^4, R^5, and R^6 are hydrogen;

- R^7 is methyl;

- R^2 is hydrogen or cyclohexyl; and

- R^3 is hydroxyl, pyridyl,

, or

5

At present, most preferred of the compounds of formula (I) is (S) 3-(1H-Indol-3-yl)-N-[1-(5-methoxy-pyridin-2-yl)-cyclohexylmethyl]-2-methyl-2-[3-(4-nitro-phenyl)-ureido]-propionamide (also referred to as Compound **1**) and its

10   pharmaceutically acceptable salts.

Other preferred compounds of Formula (I) are set out below and included also are their pharmaceutically acceptable salts:

(S) *N*-cyclohexylmethyl-2-[3-(2,6-diisopropyl-phenyl)-ureido]-3-(1*H*-indol-3-yl)-

15   2-methyl-propionamide;

N-cyclohexylmethyl-2-[3-(2,6-diisopropyl-phenyl)-ureido]-3-(1*H*-indol-3-yl)-
N-methyl-propionamide;

N-cyclohexylmethyl-2-[3-(2,6-diisopropyl-phenyl)-1-methyl-ureido]-3-(1*H*-
indol-3-yl)-propionamide;

20   2-[3-(2,6-diisopropyl-phenyl)-ureido]-2-methyl-3-(1-oxy-pyridin-2-yl)-*N*-(1-
pyridin-2-yl-cyclohexylmethyl)-propionamide;

2-[3-(2,6-diisopropyl-phenyl)-ureido]-2-methyl-3-pyridin-2-yl-*N*-(1-pyridin-2-
yl-cyclohexylmethyl)-propionamide;

2-[3-(2-*tert*-butyl-phenyl)-ureido]-*N*-cyclohexylmethyl-3-(1*H*-indol-3-yl)-2-

25   methyl-propionamide;

N-cyclohexylmethyl-2-[3-(2,6-dichloro-phenyl)ureido]-3-(1*H*-indol-3-yl)-2-
methyl-propionamide;

N-cyclohexylmethyl-2-[3-(2,6-dimethoxy-phenyl)ureido]-3-(1*H*-indol-3-yl)-2-methyl-propionamide;

N-cyclohexylmethyl-2-[3-(2,6-dimethylamino-phenyl)-ureido]-3-(1*H*indol-3-yl)-2-methyl-propionamide;

5   (S) *N*-cyclohexylmethyl-3-(1*H*-indol-3-yl)-2-methyl-2-[3-(4-nitro-phenyl)-ureido]-propionamide;

N-cyclohexylmethyl-2-[3-(2,2-dimethyl- 1 -phenyl)propyl)-ureido]-3-(1*H*-indol-3-yl)-2-methyl-propionamide;

[S-(R*, R*)] 3-(1*H*-indol-3-yl)-2-methyl-2-{3-[1-(4-nitro-phenyl)-ethyl]-

10   ureido}-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

N-(2,2-dimethyl-4-phenyl-[1,3]dioxan-5-yl)-3-(1*H*-indol-3-yl)-2-methyl-2-[3-(1-phenyl-cyclopentylmethyl)ureido]-propionamide;

(S)-*N*-(2,6-diisopropyl-phenyl)-2-[3-(2,2-dimethyl-1-phenyl-propyl)-ureido]-3-(1*H*-indol-3-yl)-propionamide;

15   (R)-*N*-(2,6-diisopropyl-phenyl)-2-[3-(2,2-dimethyl-1-phenyl-propyl)-ureido]-3-(1*H*-indol-3-yl)-propionamide;

2-[3-(2,6-diisopropyl-phenyl)-ureido]-*N*-(2,2-dimethyl-4-phenyl-[1,3]dioxan-5-yl)-3-(1*H*-indol-3-yl)-2-methyl-propionamide;

N-cyclohexyl-2-[3-(2,6-diisopropyl-phenyl)-ureido]-3-(1*H*-indol-3-yl)-2-

20   methyl-propionamide;

N-(2-cyclohexyl-ethyl)-2-[3-(2,6-diisopropyl-phenyl)-ureido]-3-(1*H*-indol-3-yl)-2-methyl-propionamide;

2-[3-(2,6-diisopropyl-phenyl)-ureido]-3-(1*H*-indol-3-yl)-2-methyl-propionamide;

25   2-[3-(2,6-diisopropyl-phenyl)-ureido]-3-(1*H*-indol-3-yl)-2-methyl-*N*-(3-methyl-butyl)-propionamide;

2-[3-(2,6-diisopropyl-phenyl)-ureido]-3-(1*H*-indol-3-yl)-2-methyl-*N*-(3-phenyl-propyl)-propionamide;

2-[3-(2,6-diisopropyl-phenyl)-ureido]-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1,2,3,4-

30   tetrahydro-naphthalen-1-yl)-propionamide;

2-[3-(2,6-diisopropyl-phenyl)-ureido]-3-(1*H*-indol-3-yl)-2-methyl-*N*-(2-phenyl-cyclohexyl)-propionamide;

2-[3-(2,6-diisopropyl-phenyl)-ureido]-*N*-indan-1-yl-3-(1*H*-indol-3-yl)-2-methyl-propionamide;

2-[3-(2,6-diisopropyl-phenyl)-ureido]-*N*-(1-hydroxy-cyclohexylmethyl)-3-(1*H*-indol-3-yl)-2-methyl-propionamide;

5   2-[3-(2,6-diisopropyl-phenyl)-ureido]-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

2-[3-(2,6-diisopropyl-phenyl)-ureido]-3-(1*H*-indol-3-yl)-2-methyl-*N*-(6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-yl)-propionamide;

2-[3-(2,6-diisopropyl-phenyl)-ureido]-3-(1*H*-indol-3-yl)-2-methyl-*N*-phenyl-
10   propionamide;

N-(1-hydroxy-cyclohexylmethyl)-3-(1*H*-indol-3-yl)-2-methyl-2-[3-(4-nitro-phenyl)-ureido]-propionamide;

2-[3-(4-cyano-phenyl)-ureido]-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

15   (S) 3-(1*H*-indol-3-yl)-2-methyl-2-[3-(4-nitro-phenyl)-ureido]-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S) 3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-2-[3-(4-trifluoromethyl-phenyl)-ureido]-propionamide;

(S) 4-(3-{2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-
20   carbamoyl]-ethyl}-ureido)-benzoic acid ethyl ester;

2-[3-(2,6-diisopropyl-phenyl)-ureido]-3-(1*H*-imidazol-4-yl)-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

2-[3-(2,6-diisopropyl-phenyl)-ureido]-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-3-(2-trifluoromethyl-phenyl)-propionamide;

25   2-[3-(2,6-diisopropyl-phenyl)-ureido]-2-methyl-3-(2-nitro-phenyl)-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S) 3-(1*H*-indol-3-yl)-*N*-[1-(5-methoxy-pyridin-2-yl)-cyclohexylmethyl]-2-methyl-2-[3-(4-nitro-phenyl)-ureido]-propionamide; and

N-cyclohexylmethyl-2-[3-(2,6-diisopropyl-phenyl)-ureido]-2-methyl-3-
30   pyridin-2-yl-propionamide.

Another preferred genus of compounds which can be used for the present purpose is of formula (II) and includes pharmaceutically acceptable salts thereof:

$$(Ar)_r - (CH_2)_j - (X)_q - (CH_2)_k - \overset{\overset{\displaystyle R^3}{|}}{\underset{\underset{\displaystyle Ar^1}{}}{N}} - \overset{\overset{\displaystyle R^5}{|}}{C} - \overset{}{\underset{\underset{\displaystyle O}{\|}}{C}} - \overset{\overset{\displaystyle R^4}{|}}{N} - (CH_2)_l - \overset{\overset{\displaystyle R^1}{|}}{\underset{\underset{\displaystyle R^6}{|}}{(C)_m}} - (CH_2)_n - R^2 \quad \text{(II)}$$
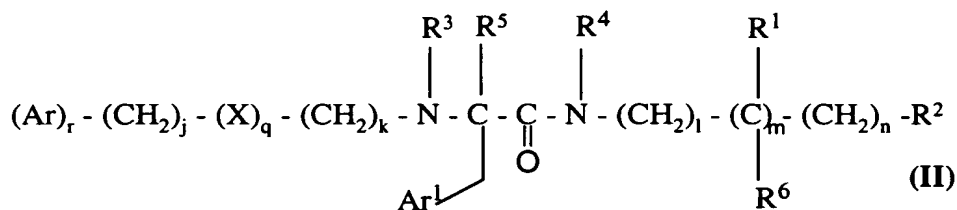
wherein:

- j is 0, 1 or 2;

- k is 0 or 1;

- l is 0, 1, 2, or 3;

- m is 0 or 1;

- n is 0, 1 or 2;

- q is 0 or 1;

- r is 0 or 1; when r is 0, Ar is replaced by hydrogen;

- Ar is phenyl, pyridyl, pyrimidyl, thienyl, furyl, imidazolyl, pyrrolyl or thiazolyl each unsubstituted or substituted by from 1 to 3 substituents selected from acetyl, alkoxy, alkyl, amino, cyano, halo, hydroxy, nitro, sulfonamido, sulfonyl, $-CF_3$, $-OCF_3$, $-CO_2H$, $-CH_2CN$, $-SO_2CF_3$, $-CH_2CO_2H$ and -$(CH_2)_sNR^7R^8$ wherein s is 0, 1, 2 or 3 and R^7 and R^8 are each independently selected from H, straight or branched alkyl of up to 6 carbon atoms, or R^7 and R^8 together with the nitrogen atom to which they are linked can form a 5- to 7-membered aliphatic ring which may contain 1 or 2 oxygen atoms;

- R^1 is hydrogen, straight or branched alkyl of up to 6 carbon atoms or cycloalkyl of between 5 and 7 carbon atoms which may contain 1 or 2 nitrogen or oxygen atoms;

- R^6 is hydrogen, methyl, or forms with R^1 an aliphatic ring of from 3 to 7 atoms which can contain an oxygen or nitrogen atom, or together with R^1 is a carbonyl group;

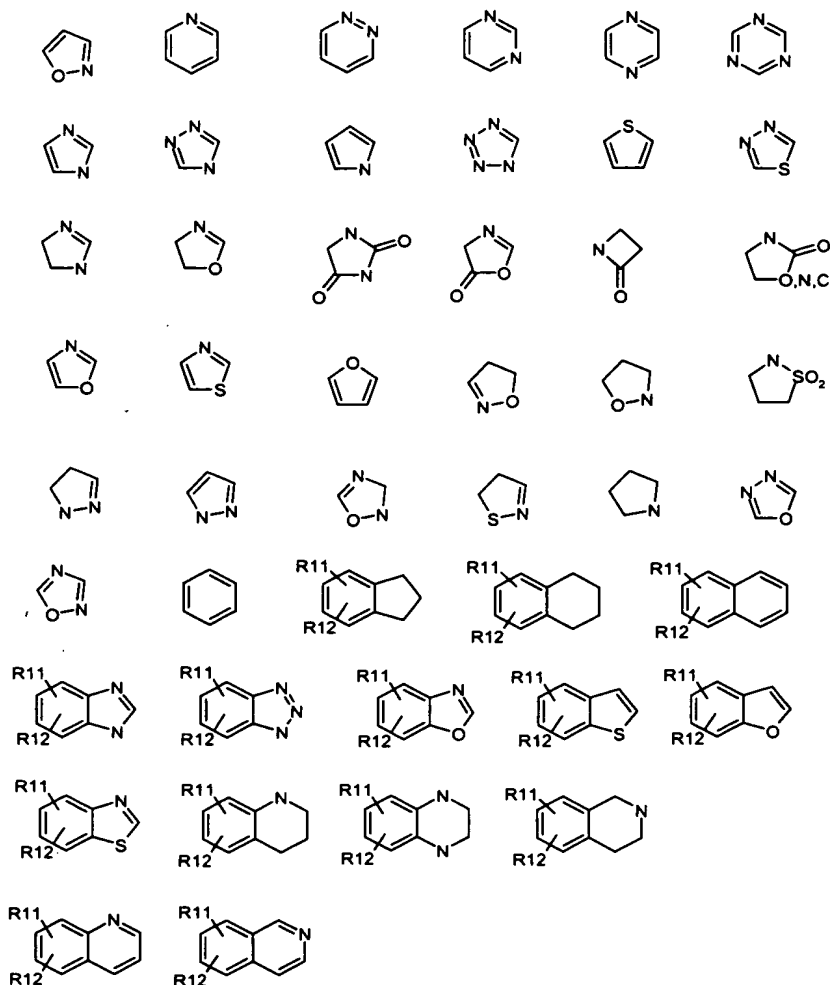- Ar^1 is independently selected from Ar or is indolyl or pyridyl-N-oxide;

- R^3, R^4, and R^5 are each independently selected from hydrogen and lower alkyl;

- R^2 is independently selected from Ar or is hydrogen, hydroxy, alkoxy, -NMe$_2$, -CONR^{9}R^{10} wherein R^9 and R^{10} are each independently selected from hydrogen, straight or branched alkyl of up to 6 carbon atoms, or R^9 and R^{10} together with the nitrogen atom to which they are linked can form a 5-to 7-membered aliphatic ring which may contain 1 or 2 oxygen or nitrogen atoms, or R^2 is
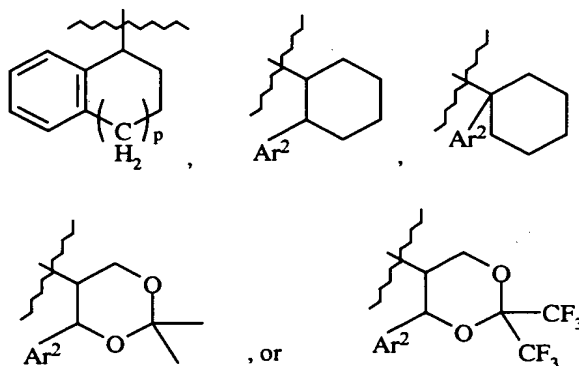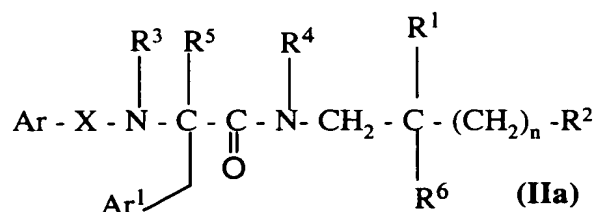

wherein p is 0, 1 or 2 and Ar^2 is phenyl or pyridyl;

- X is a divalent radical derived from any of the following

where the ring nitrogen atoms may have lower alkyl groups attached thereto, R^{11} and R^{12} are independently selected from H, halogen, hydroxy, alkoxy, acetyl, nitro, cyano, amino, CF_3 and $-(CH_2)_tNR^{13}R^{14}$ where t can be 0 or 1, R^{13} and R^{14} are each independently selected from hydrogen, straight or branched alkyl of up to 6 carbon atoms or cycloalkyl of 5 to 7 carbon atoms, containing up to 2 oxygen or nitrogen atoms.

A preferred species of compounds within the genus defined by formula (II) is represented by the formula (IIa), and includes pharmaceutically acceptable salt thereof:

$$\text{Ar - X - N - }\overset{\overset{\displaystyle R^3}{|}}{\underset{\underset{\displaystyle Ar^1}{|}}{C}} - \overset{\overset{\displaystyle R^5}{|}}{\underset{\underset{\displaystyle O}{\|}}{C}} - \overset{\overset{\displaystyle R^4}{|}}{N} - CH_2 - \overset{\overset{\displaystyle R^1}{|}}{\underset{\underset{\displaystyle R^6}{|}}{C}} - (CH_2)_n - R^2 \qquad \textbf{(IIa)}$$

wherein:

- n is 0 or 1;

- Ar is phenyl or pyridyl which may be unsubstituted or substituted with from 1 to 3 substituents selected from halogen, alkoxy, nitro and cyano;

- Ar^1 is independently selected from Ar or is pyridyl-*N*-oxide or indolyl;

- R^6 forms with R^1 an aliphatic ring of from 3 to 7 atoms which can contain an oxygen or nitrogen atom, or together with R^1 is a carbonyl group;

- R^2 is independently selected from Ar or is hydrogen, hydroxy, alkoxy, dimethylamino, tetrazolyl or -$CONR^9R^{10}$ wherein R^9 and R^{10} are each independently selected from hydrogen or methyl or R^2 is any of
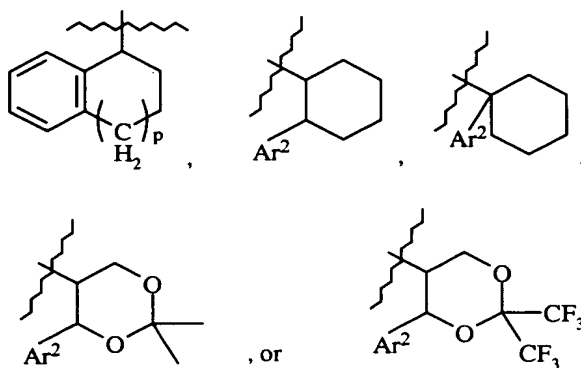
wherein p is 0, 1 or 2 and Ar^2 is phenyl or pyridyl;

- R^3, R^4 and R^5 are each independently selected from hydrogen and methyl; and
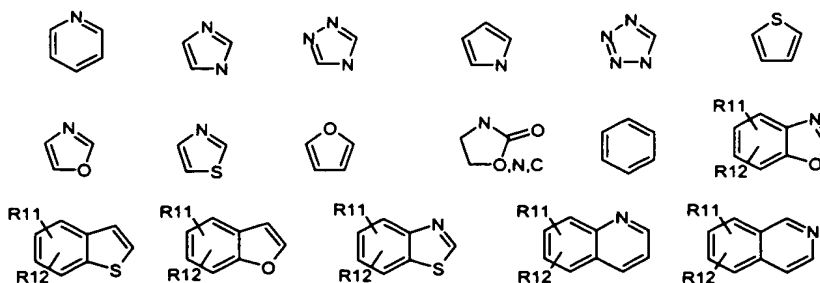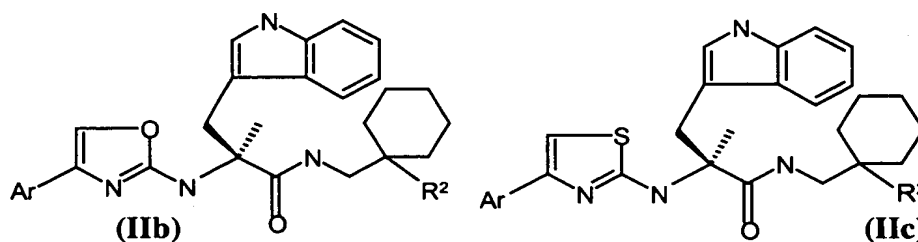
- X is selected from:

R^{11} and R^{12} being independently selected from H, halogen, hydroxy, alkoxy, acetyl, nitro, cyano, amino, CF_3 and $(CH_2)_t NR^{13}R^{14}$ wherein t is 0 or 1 and R^{13} and R^{14} are independently selected from hydrogen and methyl.

A sub-species of preferred compounds within the general formula (II) has the formula (IIb) or (IIc):

(IIb)   **(IIc)**

wherein Ar and R^2 independently represent phenyl or pyridyl which may be unsubstituted or substituted with from 1 to 3 substituents selected from halogen, alkoxy, nitro and cyano, and pharmaceutically acceptable salts thereof.

A particularly preferred compound falling within formula (II) is (S)-3-(1*H*-indol-3-yl)-*N*-[1-(5-methoxy-pyridin-2-yl)-cyclohexylmethyl]-2-methyl-2-[4-(4-nitro-phenyl)-oxazol-2-ylamino]-propionamide (also referred to as Compound **2**) and its pharmaceutically acceptable salts.

Other preferred compounds falling within formula (II) are set out below and included also are their pharmaceutically acceptable salts:

(S)-3-(1*H*-indol-3-yl)-*N*-(1-methoxymethyl-cyclohexylmethyl)-2-methyl-2-[4-(4-nitro-phenyl)-oxazol-2-ylamino]-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-2-[4-(4-nitro-phenyl)-oxazol-2-ylamino]-*N*-(2-oxo-2-phenyl-ethyl)-propionamide;

5   (S)-*N*-[1-(5-methoxy-pyridin-2-yl)-cyclohexylmethyl]-2-methyl-2-[4-(4-nitro-phenyl)-oxazol-2-ylamino]-3-phenyl-propionamide;

(S)-2-[4-(4-cyano-phenyl)-oxazol-2-ylamino]-3-(1*H*-indol-3-yl)-*N*-[1-(5-methoxy-pyridin-2-yl)-cyclohexylmethyl]-2-methyl-propionamide;

(S)-3-(1*H*-indol-3-yl)-*N*-[1-(5-methoxy-pyridin-2-yl)-cyclohexylmethyl]-2-

10   methyl- 2-(4-phenyl-oxazol-2-ylamino)-propionamide;

(S)-2-(4-ethyl-oxazol-2-ylamino)-3-(1*H*-indol-3-yl)-*N*-[1-(5-methoxy-pyridin-2-yl)-cyclohexylmethyl]-2-methyl-propionamide;

(S)-3-(1*H*-indol-3-yl)-*N*-[1-(5-methoxy-pyridin-2-yl)-cyclohexylmethyl]-2-methyl-2-[4-(4-nitro-phenyl)-thiazol-2-ylamino]-propionamide;

15   (S)-2-(benzooxazol-2-ylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-2-(pyridin-4-ylamino)-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-(isoquinol-4-ylamino)-2-methyl-*N*-(1-pyridin-2-yl-

20   cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-2-(pyrimidin-5-ylamino)-propionamide;

(S)-2-(biphenyl-2-ylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

25   (S)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-2-*m*-tolylamino-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-2-(6-phenyl-pyridin-2-ylamino)-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(R)-3-phenyl-2-phenylamino-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-
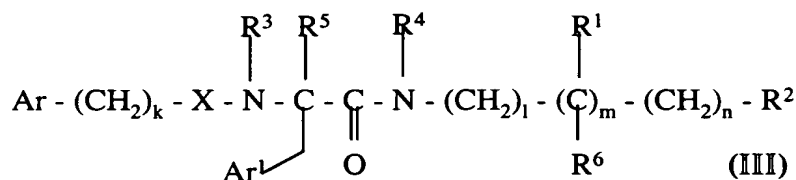
30   propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-2-phenylethylamino-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-[(benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide, and

(S)-3-(1H-indol-3-yl)-2-methyl-2-(4-nitro-benzylamino)-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide.

A third genus of bombesin receptor antagonists according to the invention has the formula (III) and include pharmaceutically acceptable salts thereof:

$$Ar - (CH_2)_k - X - N - \underset{\underset{Ar}{|}}{C} - \underset{\underset{O}{\parallel}}{\overset{\overset{R^5}{|}}{C}} - N - (CH_2)_l - \underset{\underset{R^6}{|}}{(C)_m} - (CH_2)_n - R^2$$

with R^3 on the first N and R^4 on the second N and R^1 on the $(C)_m$ carbon.   (III)

wherein:

- k is 0, 1 or 2;

- l is 0, 1, 2 or 3;

- m is 0 or 1;

- n is 0, 1 or 2;

- X is -CO-, -OCO, -SO- and -SO$_2$-;

- Ar is benzimidazolyl, benzofuryl, benzothiadiazolyl, benzothiazolyl, benzothienyl, benzopyrazinyl, benzotriazolyl, benzoxadiazolyl, furyl, imidazolyl, indanyl, indolyl, isoquinolyl, isoxazolyl, naphthyl, oxazolyl, phenyl, pyrazinyl, pyrazolyl, pyridyl, pyridazinyl, pyrimidyl, pyrrolyl, quinolinyl, tetralinyl, tetrazolyl, thiazolyl, thienyl or triazolyl each unsubstituted or substituted with from 1 to 3 substituents selected from amino, acetyl, alkyl (straight chain or branched with from 1 to 6 carbon atoms), alkoxy, cyano, halogen, hydroxy, nitro, phenyl, pyridyl, pyrrolyl, isoxazolyl, phenoxy, tolyloxy, - CF$_3$, -OCF$_3$, -SO$_2$CF$_3$, -NHCONH$_2$, -CO$_2$H, -CH$_2$CO$_2$H, -CH$_2$CN, SO$_2$Me, SO$_2$NH$_2$, SO$_2$Ph, -(CH$_2$)$_q$NR^{7}R^8, -CONR^{9}R^{10}, and CO$_2$R^{11}, wherein q is 0, 1 or 2 and R^7, R^8, R^9, R^{10}, R^{11} are each independently selected from hydrogen or straight or branched alkyl of up to 6 carbon atoms or cyclic alkyl of between 5 to 7 atoms which may contain 1 or 2 oxygen or nitrogen atoms or R^7 and R^8 or R^9 and R^{10} together with the nitrogen atom to which

they are linked can form a 5- to 7-membered aliphatic ring which may contain 1 or 2 oxygen or nitrogen atoms;

o Ar^1 is independently selected from Ar and can also be pyridyl-*N*-oxide;

o R^1 is hydrogen or straight or branched alkyl of up to 6 carbon atoms or cyclic alkyl of between 5 and 7 atoms which may contain 1 or 2 oxygen or nitrogen atoms;

o R^2 is independently selected from Ar or is hydrogen, hydroxy, alkoxy, $-NMe_2$, $-CONR^{12}R^{13}$,
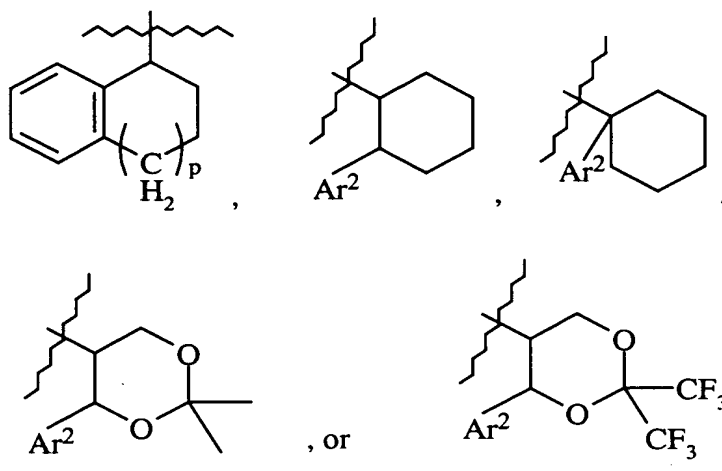
wherein p is 0, 1 or 2, Ar^2 is phenyl or pyridyl; and, R^{12} and R^{13} are each independently selected from hydrogen, straight or branched alkyl of up to 6 carbon atoms or cyclic alkyl of between 5 and 7 carbon atoms;

o R^3, R^4 and R^5 are each independently selected from hydrogen and lower alkyl; and

o R^6 is hydrogen, methyl or forms with R^1 a ring of from 3 to 7 carbon atoms which can contain an oxygen or nitrogen atom, or R^1 and R^6 can together be carbonyl.

In a preferred group of the compounds of formula (III):

o k is 0 or 1;

o l is 1;

o m is 0 or 1;

o n is 0 or 1;

- X is -C(O)-, -OC(O)-, or -SO$_2$-;
- Ar is benzofuryl, furyl, indolyl, isoquinolyl, naphthyl, phenyl, pyridyl, quinolyl or thienyl each unsubstituted or substituted with 1 or 2 substituents selected from alkoxy, cyano, halogen, nitro, phenyl, phenoxy, -CF$_3$, -(CH$_2$)$_q$NR^{7}R^8, wherein R^7 and R^8 can form a ring of between 5 to 7 atoms which may contain 1 or 2 oxygen or nitrogen atoms, or R^7 and R^8 can be independently selected from hydrogen, straight or branched alkyl of up to 4 carbon atoms or cyclic alkyl of 5 carbon atoms;
- Ar^1 is independently selected from Ar, preferably indolyl, and can also be pyridyl-N-oxide;
- R^1 and R^6 can form a cyclic alkyl of from 5 to 7 carbon atoms or R^1 and R^6 together are carbonyl;
- R^2 is independently selected from unsubstituted or substituted pyridyl or is hydrogen, hydroxy, alkoxy, -NMe$_2$, -CONR^{12}R^{13} wherein R^{12} and R^{13} are each independently selected from H and CH$_3$;
- R^3, R^4 and R^5 are each independently selected from hydrogen and methyl.

In another preferred group of the compounds of Formula (III),

- l is 1;
- m is 1;
- n is 0;
- R^2 is 2-pyridyl;
- R^6 forms a cyclohexyl with R^1.

A particularly preferred group of compounds is of formula (IIIa):

Ar - (CH$_2$)$_k$ -X- NH$\cdots$ ... (IIIa)
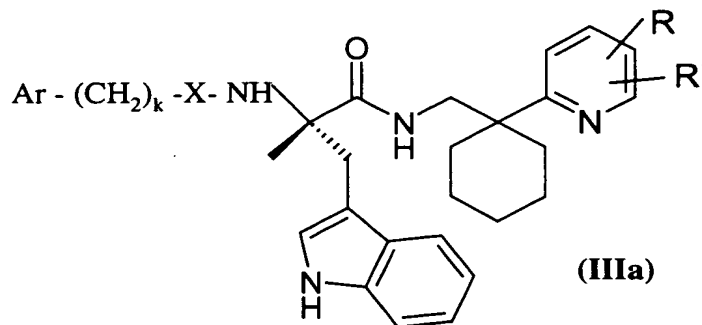
wherein Ar, k and X have the meanings given above in first, and the pyridine ring is optionally substituted by with 1 or 2 substituents, R and R', independently selected from alkoxy, cyano, halogen, nitro, phenyl, phenoxy, - CF$_3$, -(CH$_2$)$_q$NR^{7}R^8, wherein R^7 and R^8 together with the nitrogen atom to which they are linked can form a 5- to 7-membered aliphatic ring which may contain 1 or 2 oxygen or nitrogen atoms, or R^7 and R^8 can be independently selected from hydrogen or cyclic alkyl of between 5 to 7 carbon atoms, and their pharmaceutically acceptable salts thereof.

In a further set of compound (IIIa), Ar is benzofuryl, furyl, indolyl, isoquinolyl, naphthyl, phenyl, pyridyl, quinolyl or thienyl each unsubstituted or substituted with 1 or 2 substituents selected from alkoxy, cyano, halogen, nitro, phenyl, phenoxy, -CF$_3$, -(CH$_2$)$_q$NR^{7}R^8, wherein R^7 and R^8 can form a ring of between 5 to 7 atoms which may contain 1 or 2 oxygen or nitrogen atoms, or R^7 or R^8 can be a independently selected from hydrogen or cyclic alkyl of 5 carbon atoms, and X is –C(O)-, -OC(O)- or –SO$_2$.

Preferred *N*-terminal amide derivatives of the compounds of formula (III)

Amongst *N*-terminal amide derivatives, i.e. compounds of formula (III) wherein X is -C(O)-, the following compounds are most preferred:

N-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-4-nitro-benzamide;

C-dimethylamino-*N*-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-benzamide;

1*H*-indole-2-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

benzo[b]thiophene-2-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

1*H*-indole-5-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide; and

5   1*H*-indole-2-carboxylic acid ((S)-2-(1*H*-indol-3-yl)-1-{[1-(5-methoxy-pyridin-2-yl)-cyclohexylmethyl]-carbamoyl}-1-methyl-ethyl)-amide.

Other preferred *N*-terminal amide derivatives of formula (III) include the following:

10   *N*-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-benzamide;

N-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-4-methyl-benzamide;

4-chloro-*N*-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-

15   cyclohexylmethyl)-carbamoyl]-ethyl}-benzamide;

N-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-4-methoxy-benzamide;

N-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-4-methanesulfonyl-benzamide;

20   3-cyano-*N*-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-benzamide;

3-chloro-*N*-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-benzamide;

N-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-

25   carbamoyl]-ethyl}-3-methoxy-benzamide;

N-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-3-methanesulfonyl-benzamide;

dimethylamino-*N*-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-benzamide;

30   *N*-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-3-methyl-benzamide;

2-chloro-*N*-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-

cyclohexylmethyl)-carbamoyl]-ethyl}-benzamide;

N-{(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-2-nitro-benzamide;

N-{(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-2-methoxy-benzamide;

N-{(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-2-methyl-benzamide;

2-fluoro-N-{(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-benzamide;

(S)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-2-(2-p-tolyl-ethanoylamino)-propionamide;

(S)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-2-(2-o-tolyl-ethanoylamino)-propionamide;

(S)-2-[2-(4-hydroxy-phenyl)-ethanoylamino]-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-[2-(3-hydroxy-phenyl)-ethanoylamino]-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-2-(2-m-tolyl-ethanoylamino)-propionamide;

(S)-2-[2-(2-fluoro-phenyl)-ethanoylamino]-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-2-(2-thiophen-3-yl-ethanoylamino)-propionamide;

N-{(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-isonicotinamide;

furan-3-carboxylic acid {(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

furan-2-carboxylic acid {(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

5-methyl-isoxazole-3-carboxylic acid {(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

1-methyl-1H-pyrrole-2-carboxylic acid {(S)-2-(1H-indol-3-yl)-1-methyl-1-

[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

thiophene-2-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

thiophene-3-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-

5   yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

1*H*-indole-6-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

1*H*-indole-5-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

10   1*H*-indole-4-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

1*H*-indole-7-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

1-methyl-1*H*-indole-2-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-

15   pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

benzothiazole-6-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

1*H*-benzotriazole-5-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

20   3-methyl-thiophene-2-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

5-methyl-thiophene-2-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

6-methyl-pyridine-2-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-

25   pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

isoquinoline-3-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

quinoxaline-2-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

30   quinoline-8-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

5-phenyl-oxazole-4-carboxylic acid {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-

pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide;

(S)-3-(1*H*-indol-3-yl)-2-[2-(4-methoxy-phenyl)-ethanoylamino]-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-[2-(4-dimethylamino-phenyl)-ethanoylamino]-3-(1*H*-indol-3-yl)-2-

5   methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-2-[2-(2-nitro-phenyl)-ethanoylamino]-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-[2-(2-methoxy-phenyl)-ethanoylamino]-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide; and

10   *N*-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-2-pyrrol-1-yl-benzamide.

Preferred *N*-terminal urethane derivatives of the compounds of formula (III)

15   Amongst *N*-terminal urethane derivatives, i.e. compounds of formula III wherein X is –OC(=O)- , the following compounds are particularly preferred:

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid naphthalen-1-ylmethyl ester;

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-

20   carbamoyl]-ethyl}-carbamic acid 3,4-dichloro-benzyl ester;

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 3-nitro-benzyl ester;

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 3-trifluoromethyl-benzyl ester;

25   {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid quinolin-6-ylmethyl ester;

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 4-nitro-benzyl ester; and

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-

30   carbamoyl]-ethyl}-carbamic acid 3-cyano-benzyl ester.

Other preferred *N*-terminal urethane derivatives of formula (III) include the following:

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 3,4-dimethoxy-benzyl ester;

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid naphthalen-2-ylmethyl ester;

5   {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid indan-2-yl ester;

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 4-methoxy-benzyl ester;

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 4-chloro-benzyl ester;

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 2-fluoro-benzyl ester;

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 2-chloro-benzyl ester;

15   {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 4-nitro-benzyl ester;

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 2-methyl-benzyl ester;

20   {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 4-tert-butyl-benzyl ester;

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 2-methoxy-benzyl ester;

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 4-trifluoromethyl-benzyl ester;

25   {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 3-ethoxy-benzyl ester;

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 3-cyano-benzyl ester;

30   {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 2,4-dichloro-benzyl ester;

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 3-methyl-benzyl ester;

{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 3-phenoxy-benzyl ester;

35   {(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 4-methyl-benzyl ester; and

{(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 2,3-dichloro-benzyl ester.

Preferred N-terminal sulfonamide derivatives of the compounds of formula (III)

Amongst N-terminal sulfonamide derivatives of formula (III) (compounds of formula (III) wherein X is -SO$_2$-) the following compounds are particularly preferred:

(S)-3-(1H-indol-3-yl)-2-methyl-2-phenylmethanesulfonylamino-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(2-chloro-benzenesulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1H-indol-3-yl)-2-methyl-2-(naphthalene-1-sulfonylamino)-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-2-(quinoline-8-sulfonylamino)-propionamide;

(S)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-2-(2-trifluoromethyl-benzenesulfonylamino)-propionamide;

(S)-2-(biphenyl-2-sulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1H-indol-3-yl)-2-methyl-2-(5-methyl-2-phenoxy-benzenesulfonyl-amino)-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide; and

(S)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-2-(2-p-tolyloxy-benzenesulfonylamino)-propionamide.

Further preferred N-terminal sulfonamide derivatives of formula (III) include the following:

(S)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-2-(toluene-4-sulfonylamino)-propionamide;

(S)-3-(1H-indol-3-yl)-2-methanesulfonylamino-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(2-fluoro-benzenesulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(4-chloro-benzenesulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-2-(2,2,2-trifluoro-ethanesulfonylamino)-propionamide;

(S)-2-(5-dimethylamino-naphthalene-1-sulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-2-(naphthalene-2-sulfonylamino)-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

5   (S)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-2-(thiophene-2-sulfonylamino)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-2-(3-nitro-benzenesulfonylamino)-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(4-fluoro-benzenesulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-
10   pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-2-(4-nitro-benzenesulfonylamino)-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-2-(3-trifluoromethyl-benzenesulfonylamino)-propionamide;

15   (S)-2-(3,4-dichloro-benzenesulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(3-fluoro-benzenesulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-2-(4-
20   trifluoromethyl-benzenesulfonylamino)-propionamide;

(S)-2-(5-chloro-thiophene-2-sulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(3-chloro-benzenesulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

25   (S)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-2-(toluene-3-sulfonylamino)-propionamide;

(S)-2-(3,4-dimethoxy-benzenesulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(4-cyano-benzenesulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-
30   pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(2-cyano-benzenesulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(5-chloro-1,3-dimethyl-1*H*-pyrazole-4-sulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

35   (S)-2-(3,5-dimethyl-isoxazole-4-sulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(benzo[1,2,5]thiadiazole-4-sulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-
N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-2-(1-methyl-1*H*-imidazole-4-sulfonylamino)-
N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

5   (S)-2-(benzo[1,2,5]oxadiazole-4-sulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-
N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

3-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-
carbamoyl]-ethylsulfamoyl}-thiophene-2-carboxylic acid methyl ester;

(S)-3-(1*H*-indol-3-yl)-2-(5-isoxazol-3-yl-thiophene-2-sulfonylamino)-2-

10   methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-2-(2-nitro-phenylmethanesulfonylamino)-*N*-
(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(3-cyano-benzenesulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-
pyridin-2-yl-cyclohexylmethyl)-propionamide;

15   (S)-2-(1,2-dimethyl-1*H*-imidazole-4-sulfonylamino)-3-(1*H*-indol-3-yl)-2-
methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-(3-methoxy-benzenesulfonylamino)-2-methyl-*N*-(1-
pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-2-(8-nitro-naphthalene-1-sulfonylamino)-*N*-

20   (1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(2-chloro-5-nitro-benzenesulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-
(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-2-(2,4,6-
trichloro-benzenesulfonylamino)-propionamide;

25   (S)-2-(4-chloro-2-nitro-benzenesulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-
(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(5-benzenesulfonyl-thiophene-2-sulfonylamino)-3-(1*H*-indol-3-yl)-2-
methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-2-(4-

30   trifluoromethoxy-benzenesulfonylamino)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-2-(5-methyl-2-phenoxy-
benzenesulfonylamino)-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-2-(2-p-
tolyloxy-benzenesulfonylamino)-propionamide;

35   2-{(S)-2-(1*H*-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-
carbamoyl]-ethylsulfamoyl}-benzoic acid methyl ester;

(S)-2-(3-chloro-4-fluoro-benzenesulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(2,5-dichloro-thiophene-3-sulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

5   (S)-2-(3-chloro-4-methyl-benzenesulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-(2-methoxy-4-methyl-benzenesulfonylamino)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-2-(5-

10   pyridin-2-yl-thiophene-2-sulfonylamino)-propionamide;

(S)-2-(5-bromo-6-chloro-pyridine-3-sulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(2,4-dinitro-benzenesulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

15   (S)-3-(1*H*-indol-3-yl)-2-(4-methanesulfonyl-benzenesulfonylamino)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(4-*tert*-butyl-benzenesulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(2,4-dichloro-5-methyl-benzenesulfonylamino)-3-(1*H*-indol-3-yl)-2-

20   methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-2-(2-chloro-5-trifluoromethyl-benzenesulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;

(S)-3-(1*H*-indol-3-yl)-2-methyl-2-(2-nitro-4-trifluoromethyl-benzenesulfonyl-amino)-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide; and

25   (S)-2-(4-butyl-benzenesulfonylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide.

The compounds of the general formulae above are optically active. The scope of the invention therefore also includes:

30   •   All stereoisomers of the compounds of the above general formulae.

•   The solvates, hydrates and polymorphs (different crystalline lattice descriptors) of the above compounds.

•   Pharmaceutical compositions of the above compounds.

•   Prodrugs of the above compounds such as would occur to a person skilled in

35   the art; see Bundgaard et al., *Acta Pharm. Suec.*, 1987; 24: 233-246.

The alkyl groups contemplated by the invention include straight, branched, or cyclic carbon chains of from 1 to 8 carbon atoms except where specifically stated otherwise. Representative groups are methyl ethyl, propyl, isopropyl, n-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, 2-methylhexyl, n-pentyl, 1-methylbutyl, 2,2-dimethylbutyl, 2-methylpentyl, 2,2-dimethylpropyl, n-hexyl, and the like.

The lower alkyl groups include carbon chains of up to 6 carbon atoms. The cycloalkyl groups contemplated by the invention comprise those having 3 to 7 carbon atoms including cyclopentyl and cyclohexyl. They may be substituted with from 1 to 3 groups selected from halogens, nitro, alkyl, and alkoxy.

The alkoxy groups contemplated by the invention comprise both straight and branched carbon chains of from 1 to 6 carbon atoms unless otherwise stated. Representative groups are methoxy, ethoxy, propoxy, i-propoxy, t-butoxy, and hexoxy.

The term "halogen" is intended to include fluorine, chlorine, bromine, and iodine. The term "amine" is intended to include free amino, alkylated amines, and acylated amines.

The term "subject" includes animals, particularly mammals and more particularly humans.

Optical isomers and salts

The compounds of the above general formulae all have at least one chiral centre and some have multiple chiral centres depending on their structure. In particular, the compounds of the present invention may exist as diastereoisomers, mixtures of diastereoisomers, or as the mixed or the individual optical enantiomers. The present invention contemplates all such forms of the compounds. The mixtures of diastereoisomers are typically obtained as a result of the reactions described more fully below. Individual diastereoisomers may be separated from mixtures of the diastereoisomers by conventional techniques such as column chromatography or repetitive recrystallization. Individual enantiomers may be separated by conventional methods well known in the art such as conversion to a salt with an optically active

compound, followed by separation by chromatography or recrystallization and reconversion to the non-salt form.

Where it is appropriate to form a salt, the pharmaceutically acceptable salts include acetate, benzenesulfonate, benzoate, bicarbonate, bitartrate, bromide, calcium acetate, camsylate, carbonate, chloride, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycoloylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, mucate, napsylate, nitrate, pamoate (embonate), pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, sulfate, tannate, tartrate, theoclate, triethiodide, benzathine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine, procaine, aluminum, calcium, lithium, magnesium, potassium, sodium, and zinc.

Preferred salts are made from strong acids. Such salts include hydrochloride, mesylate, and sulfate.

Other non-peptide bombesin antagonists

Other non-peptide bombesin antagonists which are believed to be suitable for use in the present invention are described and claimed in the following documents, the contents of which are incorporated herein by reference: WO 00/09115, WO 00/09116, WO 92/07830, JP 07258081 and WO 98/07718.

Preparative methods for the compounds of formula (I)

Preparation of the compounds of formula (I) is described in WO 98/07718, the disclosure of which is incorporated herein by reference.

Preparative methods for compounds of formula (II)

Throughout this application the following abbreviations have the meanings listed below:
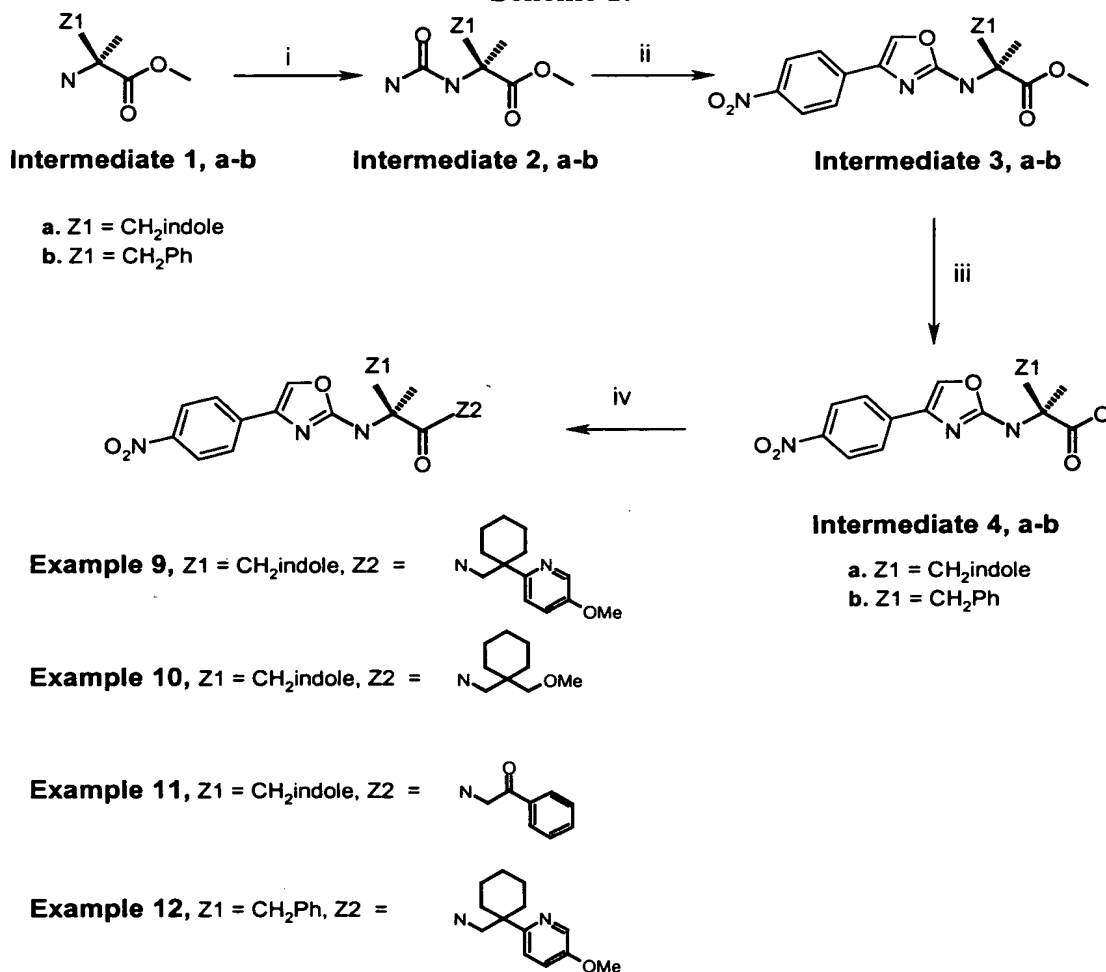
	NEt$_3$	triethylamine
5	THF	tetrahydrofuran
	HBTU	O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate
	DIPEA	N,N-diisopropylethylamine
	DMF	N,N-dimethylformamide
10	TEBA	benzyltriethylammonium chloride
	BOC2O	di-*tert*-butyl dicarbonate
	TFA	trifluoroacetic acid
	DMA	N,N-dimethylacetamide
	EtOAc	ethyl acetate
15	MeOH	methanol
	Trp	tryptophan
	Ph	phenyl
	HPLC	high pressure liquid chromatography
	NP	normal phase
20	RP	reverse phase
	DMAP	N,N-dimethyl-4-amino pyridine
	OAc	acetate
	OB	oestradiol benzoate

25   The production of compounds of the formula (II) in which X is oxazolyl is shown in Scheme 1 which illustrates the synthesis of the compounds of **Examples 9** to **12** in four steps via Intermediates **4a** or **4b**. The steps are:

- Formation of the *p*-nitrophenylcarbamate of the methyl ester (Intermediate **1**)
30   and subsequent treatment with aqueous ammonia to give a primary urea (Intermediate **2**).
- Cyclisation of the primary urea with 2-bromo-1-(4-nitro-phenyl)-ethanone to form an oxazole ring (Intermediate **3**).

- Hydrolysis of the methyl-ester-protecting group gives Intermediates **4a** or **4b**. Reaction of Intermediate **4a** or **4b** with the amine **Z2**, using HBTU to form an amide linkage, affords the desired compounds.

5

Scheme 1:

Intermediate 1, a-b **Intermediate 2, a-b** **Intermediate 3, a-b**

a. Z1 = CH$_2$indole
b. Z1 = CH$_2$Ph

iii

Intermediate 4, a-b

a. Z1 = CH$_2$indole
b. Z1 = CH$_2$Ph

Example 9, Z1 = CH$_2$indole, Z2 =

Example 10, Z1 = CH$_2$indole, Z2 =

Example 11, Z1 = CH$_2$indole, Z2 =

Example 12, Z1 = CH$_2$Ph, Z2 =

In the above scheme:

i) a) 4-Nitrophenylchloroformate, NEt$_3$, THF b) NH$_3$ aq.

ii) 2-bromo-1-(4-nitro-phenyl)-ethanone in either toluene/dioxan at reflux (**3a**) or

10 1,2-dichloroethane at reflux (**3b**)

iii) LiOH, dioxan, H$_2$O

iv)   HBTU, DIPEA, DMF, Z2

Scheme 2 describes the synthesis of the compounds of **Examples 13** to **15** from
Intermediate 2a.

5

- A primary urea **2a** is cyclised with an appropriate bromomethyl ketone
  containing the group Z3 to form an oxazole ring (Intermediate **5**).

- Hydrolysis of the methyl ester protecting group of the resulting Intermediate
  5a, 5b or **5c** gives the Intermediates **6 a-c**.

10
- Reaction of an Intermediate **6a**, **6b** or **6c** with [1-(5-methoxy-2-
  pyridyl)cyclohexyl]methanamine in the presence of HBTU to form an amide
  bond affords the desired compounds.

15   **Scheme 2:**

Intermediate 2a   **Intermediate 5, a-c**

5a, Z3 = 4-NCPhen

5b, Z3 = Phenyl-
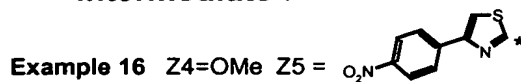
5c, Z3 = Ethyl-

Intermediate 6, a-c
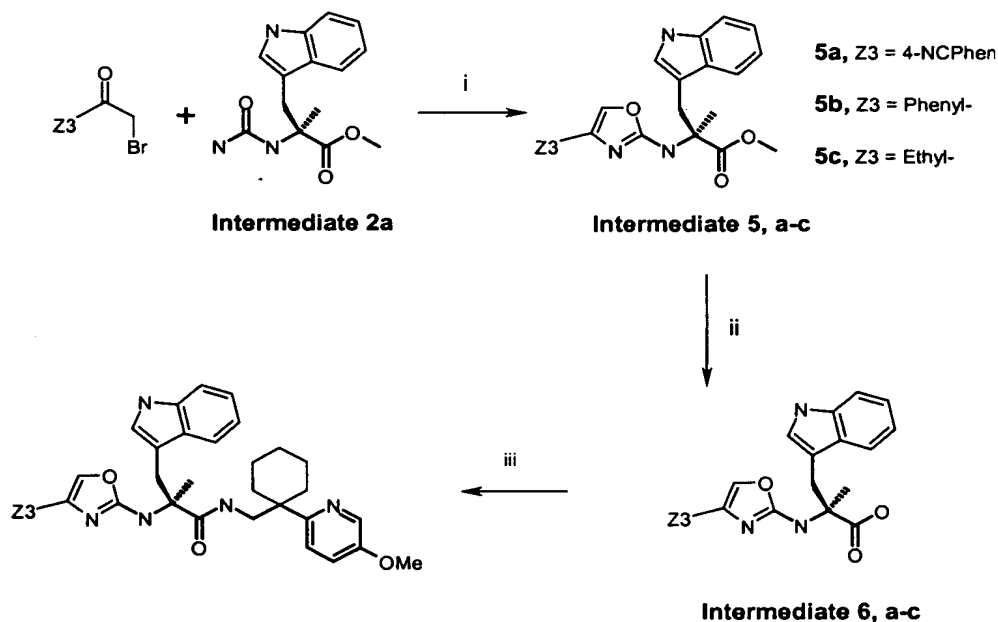
In the above scheme:

i)   DMF at 30°C

20 ii)   LiOH, dioxan, H₂O

iii)   HBTU, DIPEA, DMF, [1-(5-methoxy-2-pyridyl)cyclohexyl]methanamine
(described in WO 98/07718)

Scheme 3 describes a two step synthesis for the compounds of **Examples 16-23**. The reactions are preferentially carried out as a "one-pot" process in which:

5
- An aromatic ring of a compound Z5-Br or Z5-Cl is appended onto the N-terminal of the illustrated amino acid using a copper catalysed reaction.

- Formation of an amide linkage between the resulting acid and [1-(5-methoxy-2-pyridyl)cyclohexyl]methanamine or [1-(2-pyridyl)cyclohexyl]methylamine in the presence of HBTU affords the desired compounds.

10

Scheme 3:

Intermediate 7

Example 16   Z4=OMe Z5 =

Example 17   Z4=H   Z5 =

Example 18   Z4=H   Z5=

Example 19   Z4=H   Z5 =

Example 20   Z4=H   Z5=

Example 21   Z4=H   Z5 =

Example 22   Z4=H   Z5 =

Example 23   Z4=H   Z5 =
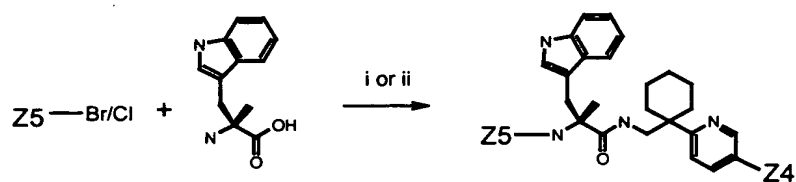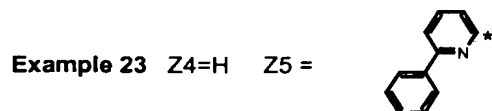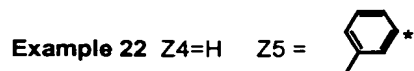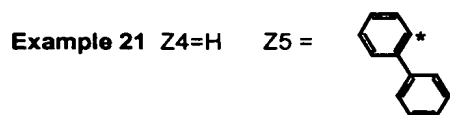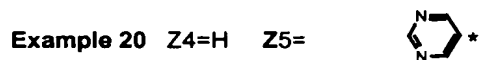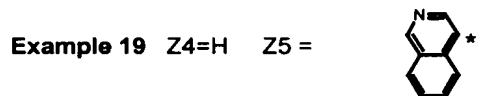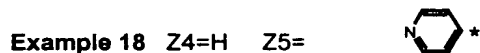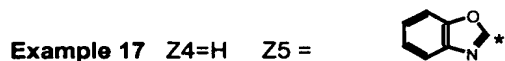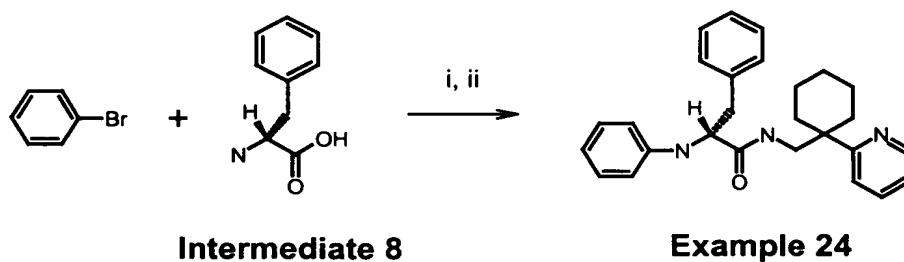
In the above scheme:

i)   a) 10% CuI, K$_2$CO$_3$, DMF, 130°C

        b) HBTU, DIPEA, DMF, and [1-(5-methoxy-2-pyridyl)cyclohexyl]methan-

        amine (described in WO 98/07718) or [1-(2-pyridyl)cyclohexyl]methylamine

        (described in WO 98/07718)

ii)   a) 5-10% CuI, K$_2$CO$_3$, TEBA, Pd(P(o-tolyl)$_3$)Cl$_2$, DMF, 130°C

        b) HBTU, DIPEA, DMF, and [1-(5-methoxy-2-pyridyl)cyclohexyl]methan-

        amine (described in WO 98/07718) or [1-(2-pyridyl)cyclohexyl]methylamine

        (described in WO 98/07718)

* represents the attachment point.

Scheme 4 describes the two step one-pot synthesis of the compound of **Example 24**:

● The aromatic ring is appended onto the N-terminal of the amino acid (Intermediate **8**) using a copper catalysed reaction and then an in situ HBTU amide bond formation reaction affords the desired compound.

Scheme 4:

Intermediate 8   **Example 24**
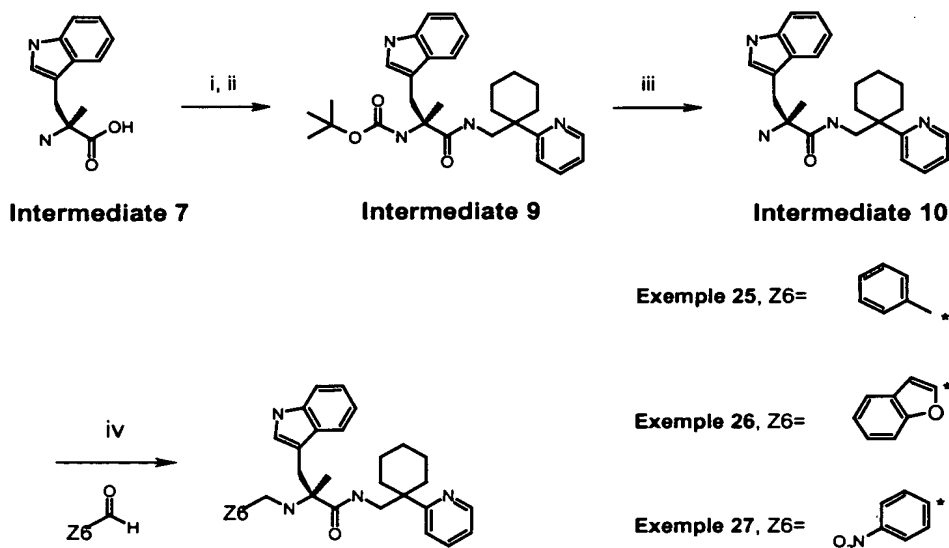

In the above scheme:

i)   10% CuI, K$_2$CO$_3$, DMA, 90°C

ii)   HBTU, NEt₃, DMA, [1-(2-pyridyl)cyclohexyl]methylamine (described in WO 98/07718)

Scheme 5 describes the synthesis of the compounds of **Examples 25 - 27** via **Intermediate 10** by the steps of :

- N-BOC protection of the amino acid (**Intermediate 7**) which provides the groups R^5 and Ar^1.

- Reaction of the protected amino acid with an amine that provides the groups R^1, R^2, R^4 and R^6 using HBTU to form an amide linkage, and thereby give the **Intermediate 9.**

- N-BOC deprotection of the **Intermediate 9** to give **Intermediate 10**.

- Reductive amination of **Intermediate 10** with the appropriate aldehyde Z6CHO to give the desired compounds.

Scheme 5:

Intermediate 7   Intermediate 9   Intermediate 10

Exemple 25, Z6=

Exemple 26, Z6=

Exemple 27, Z6=

In the above scheme:

i)   BOC$_2$O, K$_2$CO$_3$, dioxane, water

ii)   HBTU, DIPEA, [1-(2-pyridyl)cyclohexyl]methylamine (described in WO 98/07718), DMF

iii)   TFA, CH$_2$Cl$_2$

5   iv)   NaBH(OAc)$_3$, 1,2-dichloroethane.
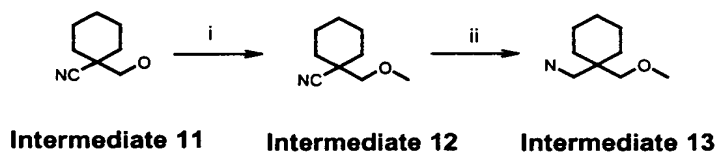

* represents the attachment point.

Scheme 6 describes the synthesis of **Intermediate 13**.

10

- The alcohol **11** is methylated using sodium hydride.

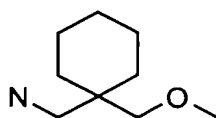- The resulting nitrile is reduced using Raney nickel under an atmosphere of hydrogen.

15   **Scheme 6:**

Intermediate 11   Intermediate 12   Intermediate 13

In the above scheme:

i)   NaH, CH$_3$I, THF

20   ii)   Raney nickel, ethanolic ammonia, H$_2$, 345 kPa

Intermediate 13

25

C-(1-methoxymethyl-cyclohexyl)-methylamine

Intermediate 13

The above compound was prepared as shown in Scheme 6.

5 1.   Sodium hydride (862mg, 21.5mmol, 60% in oil) was taken up in THF (50ml) under argon at 0°C. To this was added a solution of methyl iodide (1.34ml, 21.6mmol) and 1-hydroxy-cyclohexanecarbonitrile (1.0g, 7.18mmol; see J. Fröhlich *et al.*, *Heterocycles* 1994, 37, 1879-91) in THF (30ml) dropwise over 45 minutes. Once addition was complete the reaction mixture was stirred at room temperature overnight, 10 and then quenched with *i*-propanol followed by water (100ml). The mixture was then extracted with dichloromethane (2x150ml). The combined organic phases were dried (MgSO$_4$) and solvent removed under reduced pressure. Residue was purified by chromatography using heptane/ethyl acetate (4:1). Removal of solvent under reduced pressure gave 1-methoxymethyl-cyclohexanecarbonitrile (1.1g, 88%) as a pale yellow 15 oil.

IR (film): 2934, 2861, 2832, 2235, 1476, 1452, 1385, 1211, 1187, 1185, 1126, 1102, 978, 932, 901, 849 cm^{-1};

^{1}H NMR (CDCl$_3$): δ = 1.13-1.33 (3H, m), 1.57-1.78 (5H, m), 1.94-2.02 (2H, m), 3.36 (1H, s), 3.42 (3H, s);

20

2.   To the 1-methoxymethyl-cyclohexanecarbonitrile (1.1g, 7.2mmol) in ethanolic ammonia (60ml) was added Raney nickel catalyst (0.55g, pre-washed with water and ethanol). Reaction mixture was shaken for 16 hours under hydrogen (345 kPa) at 30°C. The catalyst was filtered off catalyst with extreme caution through a bed of 25 Kieselguhr and washed with ethanol. Removal of the solvent under reduced pressure gave **Intermediate 13** (1.12g, 99%) as a yellow oil.

MS m/e (ES+): 158.2 (M⁺ + H, 100%);

IR (film): 2926, 2857, 1572, 1452, 1378, 1316, 1190, 1140, 966 cm⁻¹;

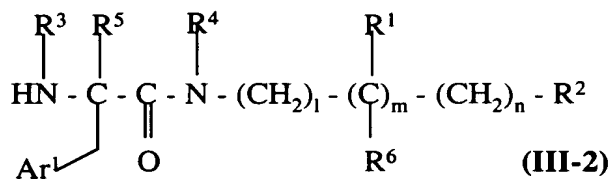^{1}H NMR (CDCl₃): δ = 1.20-1.60 (12H, m), 2.62 (2H, s), 3.23 (2H, s), 3.32 (3H, s)

Preparative methods for compounds of formula (III)

Compounds of the formula (III) in which X is –CO- can be prepared by condensing an acid of the formula (III-1)

$$Ar - (CH_2)_k\text{-COOH} \quad \textbf{(III-1)}$$

or a derivative thereof with an amine of the formula (III-2)

$$\underset{Ar^1}{\overset{R^3\ R^5\quad R^4\qquad\qquad R^1}{HN - C - C - N - (CH_2)_l - (C)_m - (CH_2)_n - R^2}}$$
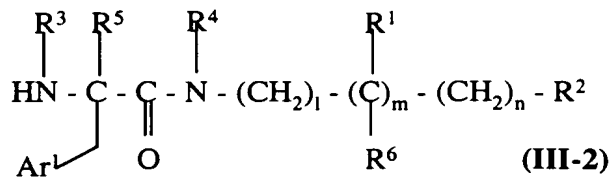$$Ar^1 \qquad O \qquad\qquad R^6 \qquad \textbf{(III-2)}$$

in an aprotic polar solvent in the presence of an appropriate catalyst, the values of the substituents Ar, Ar¹ and R¹ to R⁶ and the parameters k to n being as defined above with reference to formula (III), and optionally converting the resulting product to a pharmaceutically acceptable salt. For example, the condensation may be carried out in dimethylformamide using O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU) and N,N-diisopropyl-ethylamine (DIPEA) as catalyst.

Compounds of the formula (III) in which X is –OC(=O)- can be prepared by forming a carbonate from an alcohol of the formula (III-3)

$$Ar - (CH_2)_k\text{-OH} \quad \textbf{(III-3)}$$
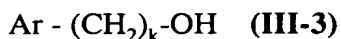
and reacting the carbonate with an amine of the formula (III-2)

$$\begin{array}{c} R^3 \quad R^5 \qquad R^4 \qquad\qquad R^1 \\ | \qquad | \qquad\quad | \qquad\qquad\quad | \\ HN - C - C - N - (CH_2)_l - (C)_m - (CH_2)_n - R^2 \\ Ar^{\diagup} \qquad O \qquad\qquad\quad R^6 \qquad\quad \textbf{(III-2)} \end{array}$$
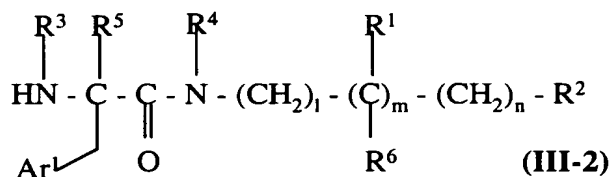
in an aprotic polar solvent in the presence of a base, the values of the substituents Ar, Ar^1 and R^1 to R^6 and the parameters k to n being as defined above with reference to

5   formula (III), and optionally converting the resulting product to a pharmaceutically acceptable salt. For example, the compound of formula (III-3) may be reacted with 4-nitrophenyl chloroformate in dichloromethane using pyridine as catalyst, and the resulting carbonate may be reacted with the amine of formula (III-2) in dimethyl formamide using N,N-dimethyl-4-amino pyridine as catalyst.

10

Compounds of the formula (III) in which X is $-SO_2-$ can be prepared by condensing a sulfonyl chloride of the formula (III-4)

$$Ar - (CH_2)_k - SO_2Cl \quad \textbf{(III-4)}$$

15

with an amine of the formula (III-2)

$$\begin{array}{c} R^3 \quad R^5 \qquad R^4 \qquad\qquad R^1 \\ | \qquad | \qquad\quad | \qquad\qquad\quad | \\ HN - C - C - N - (CH_2)_l - (C)_m - (CH_2)_n - R^2 \\ Ar^{\diagup} \qquad O \qquad\qquad\quad R^6 \qquad\quad \textbf{(III-2)} \end{array}$$

20   in an aprotic polar solvent in the presence of a base as catalyst, the values of the substituents Ar, Ar^1 and R^1 to R^6 and the parameters k to n being as defined above with reference to formula (III), and optionally converting the resulting product to a pharmaceutically acceptable salt. For example, the condensation may be carried out in dimethylformamide in the presence of N,N-diisopropylethylamine and N,N-dimethyl-

25   4-aminopyridine.

In the above methods, the amine of formula (III-2) is preferably a chiral amine of formula (III-5)

(III-5)
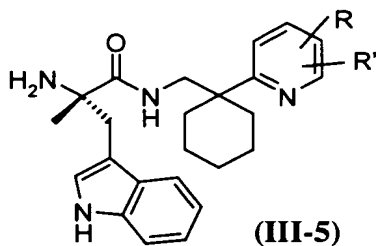
wherein the pyridine ring is optionally substituted by with 1 or 2 substituents R and R' selected from alkoxy, cyano, halogen, nitro, phenyl, phenoxy, - CF_3, - $(CH_2)_qNR^7R^8$, wherein R^7 and R^8 can form a ring of between 5 to 7 atoms, which may contain 1 or 2 oxygen or nitrogen atoms, or R^7 and R^8 can be independently selected from hydrogen or cyclic alkyl of from 1 to 5 carbon atoms, methoxy being a particularly preferred substituent, as in the chiral amine (III-6):

(III-6)
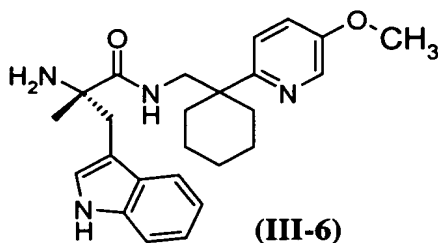
B) Peptide bombesin receptor antagonists

Bombesin antagonists which are peptides and which are believed to be suitable for use in the present invention are described in the following documents, the contents of which are incorporated herein by reference:

Publication number	Publication number
WO 97/09347	EP 0835662
US 5650395	US 5439884
WO 96/28214	WO 95/00542
EP 0737691	US 5620955
US 5767236	WO 92/02545
WO 91/04040	EP 0468497
EP 0309297	CA 2030212
EP 0438519	WO 92/20707
EP 0559756	WO 93/16105
WO 89/02897	US 4943561
WO 90/03980	US 5019647
WO 91/02746	US 5028692
WO 92/09626	US 5047502
WO 92/20363	WO 94/02018

WO 94/02163	WO 88/07551
WO 94/21674	WO 89/09232
WO 96/17617	EP 0315367
US 5084555	EP 0345990
US 5162497	US 5068222
US 5244883	US 5620959
US 5723578	UK 2231051
US 5750646	EP 0339193
US 5877277	WO 90/01037
US 5985834	WO 91/06563
EP 0428700	EP 0402852

Pharmaceutical compositions

For preparing pharmaceutical compositions from the compounds of this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, sachets, and suppositories.

A solid carrier can be one or more substances which may also act as diluents, flavouring agents, solubilizers, lubricants, suspending agents, binders, or tablet disintegrating agents; it can also be an encapsulating material. In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain 5% to about 70% of the active component. Suitable carriers are magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter, and the like.

Liquid form preparations include solutions, suspensions, and emulsions. Sterile water or water-propylene glycol solutions of the active compounds may be mentioned as an example of liquid preparations suitable for parenteral administration. Liquid preparations can also be formulated in solution in aqueous polyethylene glycol solution. Aqueous solutions for oral administration can be prepared by dissolving the active component in water and adding suitable colorants, flavouring agents,

stabilizers, and thickening agents as desired. Aqueous suspensions for oral use can be made by dispersing the finely divided active component in water together with a viscous material such as natural synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other suspending agents known to the pharmaceutical formulation art.

Preferably the pharmaceutical preparation is in unit dosage form. In such form, the preparation is divided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of the preparation, for example, packeted tablets, capsules, and powders in vials or ampoules. The unit dosage form can also be a capsule, sachet, or tablet itself, or it can be the appropriate number of any of these packaged forms.

For preparing suppository preparations, a low-melting wax such as a mixture of fatty acid glycerides and cocoa butter is first melted and the active ingredient is dispersed therein by, for example, stirring. The molten homogeneous mixture is then poured into convenient sized moulds and allowed to cool and solidify.

Compositions that are adapted for oral administration to humans are preferred, especially such compositions in unit dosage form.

Combination therapy

Without wishing to be bound by any particular theory or teaching, the inventors believe that bombesin receptor antagonists could be used as part of a medicament in combination with one or more vasodilator, hormone therapy or neurotransmitter modulator. Such products are used or tested in the treatment of sexual dysfunction. Vasodilators for the treatment of sexual dysfunctions of organic (rather than psychogenic) origin, act at the penis, clitoris or vagina level on local blood flow or lubricant secretions. Vasodilators useful for the treatment of sexual dysfunction include alprostadil or phentolamine, NO (nitric oxide) enhancers such as

L-arginine, and PDE5 inhibitors such as sildenafil or a pharmaceutically acceptable salt thereof (*Scrip's Complete Guide to Women's Healthcare*, p.194-205, 2000)(Sachs B.D., *Neuroscience and Biobehavioral Review* , 2000, 24 541-560, Benet and Melman, 1995, *Urol. Clin.N. Amer.* 22:699-709), VIP (Vaso Intestinal Peptide)

5   enhancers (*Scrip's Complete Guide to Women's Healthcare*, p.194-205, 2000) or angiotensin-2 receptor antagonists such as losartan (American Heart Association meeting, New Orleans, 2000).

Hormone therapies useful in the treatment of sexual dysfunction of

10   organic and psychogenic nature include modulators of steroid hormones, steroid hormones or hormone product (including synthetic hormones) including oestrogen (*Scrip's Complete Guide to Women's Healthcare*, p.194-205, 2000), or androgens such as testosterone (*Scrip's Complete Guide to Women's Healthcare*, p.194-205, 2000, Sachs B.D., *Neuroscience and Biobehavioral Review*, 2000, 24 541-560),

15   which act in areas of the CNS associated with sexual desire and sexual arousal (Wilson CA. *Pharmacological targets for the control of male and female sexual behaviour*. In: Sexual Pharmacology, Riley AJ, Peet M, Wilson CA (Eds), Clarendon Press, Oxford. 1993:1-58).

20   Neurotransmitter modulators useful in the treatment of both psychogenic and organic sexual dysfunction include neurotransmitter agonists and antagonists such as catecholamine agonists such as the D_2 agonist quinelorane, $5HT_2$ antagonists such as ritanserin, monoamine synthesis modifiers such as treatments that reduce endogenous 5HT activity, including inhibition of 5HT synthesis using para-

25   chlorophenylalanine, monoamine metabolism or uptake modifiers that inhibit catecholamine metabolism or reuptake, such as tricyclic antidepressants, e.g. imipramine (Wilson CA. *Pharmacological targets for the control of male and female sexual behaviour*. In: Sexual Pharmacology, Riley AJ, Peet M, Wilson CA (Eds), Clarendon Press, Oxford. 1993:1-58).

30

The use of this combination therapy includes the preparation of therapies that would allow administration of both components of the medicament, i.e. bombesin

receptor antagonists and a vasodilator, hormone therapy medicament or neurotransmitter modulator medicament in a single dose. A preferred formulation would allow oral administration. However, administration by suppository, cream, transdermal patch or injection is also part of this invention. Alternatively the inventors envisage formulations which allow administration of the bombesin receptor antagonist via a separate route to that of the vasodilator, hormone therapy medicament or neurotransmitter modulator medicament. Such routes could include for example oral administration of the bombesin receptor antagonist and transdermal patch application of the vasodilator. Thus there may be provided a kit in which unit doses of bombesin receptor antagonist occur in association with unit doses of the vasodilator, hormone therapy medicament or neurotransmitter modulator medicament. For example, in the case of a kit where bombesin receptor antagonist is formulated as a tablet capsule or other unit dosage form for oral administration and the vasodilator is provided as a transdermal patch, the two dosage forms could be provided in the form of a two-row tear-off strip in which compartments containing the tablets, etc. occur above compartments containing the transdermal patches. Other forms of packaging in which the two dosage forms are spatially associated so as to make it easy for patients to take them together and to be reminded when they have done so will readily occur to those skilled in the art. The kit will also contain instructions as to when and how the individual components of the kit should be administered.
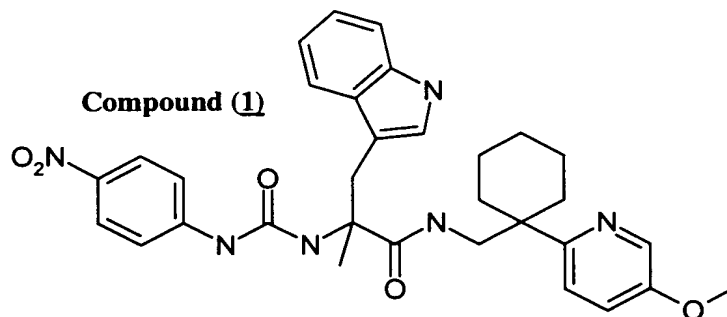
How the invention may be put into effect will now be described, by way of example only, with reference to the following examples, some of which are preparative and others of which describe results of biological tests.

Example 1

Effect of (S) 3-(1H-Indol-3-yl)-N-[1-(5-methoxy-pyridin-2-yl)-cyclohexyl-methyl]-2-methyl-2-[3-(4-nitro-phenyl)-ureido]-propionamide (Compound (1)) on female rat sexual proceptivity

Compound (1)

Ovariectomised adult female Sprague Dawley rats (180-200g, from Charles River) were housed in groups of 6 in a reversed lighting system of 12h light:dark (lights off 7.00-19.00h). Two weeks after ovariectomy they were used for sexual activity tests. The experiments started at least 5h into the dark period.

Tests were carried out in a circular arena of 90cm diameter, surrounded by a 30cm high wall. Two small cages with wire-mesh front (15x15cm) are fixed into the wall such that the front of the cage is «flush» with the wall and the 2 cages are opposite each other. They contained two stimuli animals: an intact sexually experienced male and a receptive female (ovariectomised, primed with 5μg oestradiol benzoate dissolved in corn oil and injected subcutaneously 48 hours before the test and with 0.5 mg of progesterone four hours before the test). Sexually naive test and control animals were used. Forty eight hours before the tests, both the test and control animals were primed with 5μg oestradiol benzoate. For animals used as positive controls, progesterone (0.5mg/0.1ml) was dissolved in corn oil and administered subcutaneously (s.c.), 4h before the test. Test and control animals were introduced one at a time for 10 minute periods into the arena. During the 10min test, the time that the test or positive control animal spent investigating each stimulus animal was noted. The arena was thoroughly cleaned between animals. The position of the male/female stimuli boxes was randomised between animals, in order to avoid place preference. The difference in the percentage of time spent investigating the male minus the female stimuli was calculated, out of the total time spent investigating stimuli animals.

Compound (1) was dissolved in 100% β-cyclodextrin and then diluted with saline to a final solution of 50% 2-hydroxypropyl-β-cyclodextrin. It was administered intraperitoneally (i.p.) at doses of 3 and 10mg/kg, in a dosing volume of 1ml/kg, 1h before tests. Progesterone (0.5mg/0.1ml) was dissolved in corn oil and administered subcutaneously (s.c.), 4h before test, as a positive control.

Compound (1) dose-dependently (3mg/kg-10mg/kg) increased the percentage of time spent investigating the male stimulus, with a MED of 10mg/kg (see **Figure 1**). The effect of this dose was similar to the effect of progesterone (prog). (*P<0.05, **P<0.01 Kruskal-Wallis followed by Mann-Whitney test, *vs* vehicle).

Example 2

Effect of Compound (1) on female rat sexual receptivity

Ovariectomised adult female Sprague Dawley rats (180-200g, from Charles River) were housed in groups of 6 in a reversed lighting system of 12h light:dark (lights off 7.00-19.00h). Two weeks after ovariectomy they were used for sexual activity tests. The experiments started at least 5h into the dark period.

Compound (1) was dissolved in 100% β-cyclodextrin and then diluted with saline to a final solution of 50% 2-hydroxypropyl-β-cyclodextrin. It was administered intraperitoneally (i.p.) at a dose of 10mg/kg, in a dosing volume of 1ml/kg. Quinelorane (6.25μg/kg) was dissolved in water and administered s.c. as positive control. Forty eight hours before testing, ovariectomised female rats (as described above), were primed with 5μg oestradiol benzoate dissolved in corn oil and injected subcutaneously. This is a low dose of oestrogen that does not re-establish sexual behaviour in an ovariectomised female but provides a minimum hormonal background for pharmacological agents to stimulate sexual behaviour. The females were placed with a series of vigorous male rats and subjected to 10 mounts.

The lordotic response of the animal was recorded and expressed as a percentage of the mounts (i.e. lordosis quotient, LQ), as previously described. Animals showing LQ<20 were considered non-receptive and were included in the

study. Each rat was tested prior to administration of the compound and then tested similarly post-injection. The pre-treatment times were 1h for Compound (1) and vehicle (50% β-cyclodextrin, i.p.) or 90min for quinelorane.

5   As shown in **Figure 2**, a single administration of quinelorane (6.25μg/kg, s.c.) significantly (P<0.01) increased the LQ, 90min after administration, compared to the LQ shown before administration (paired t test). A single administration of Compound (1) (10mg/kg, i.p.) also had a significant (P<0.05) stimulatory effect on the LQ, 1h after administration, compared to the LQ shown before administration (paired t test).

10

Example 3

The effect of repeated administration of Compound (1) on female rat proceptivity

15

In the present study we have investigated whether the repeated administration of a higher dose of Compound (1) (15mg/kg) still results in stimulation of proceptivity.

20   Ovariectomised adult female Sprague Dawley rats (180-200g) were housed in groups of 5 in a reversed lighting system of 12h light:dark (lights off 5.00-17.00h). They were used for the experiments at least two weeks after ovariectomy. Forty eight hours before tests, the animals were primed with oestradiol benzoate (5μg/0.1ml in corn oil, s.c.). On day 1, progesterone (0.5mg/0.1ml, in corn oil, s.c.) was

25   administered to one of the groups 4h before tests, as a positive control. Compound (1) (15mg/kg, i.p.) was administered in 50% 2-hydroxypropyl-β-cyclodextrin, 1h before tests. The test lasted 10 minutes and was carried out as described before. The difference in the percentage of time spent investigating the male minus the female stimuli was calculated, out of the total time spent investigating stimuli animals.

30   Animals were submitted to a test on day 1 and on day 15. From day 2 to 14 the Compound (1) group received a daily injection of the compound (15mg/kg, i.p.),

while both the vehicle and the progesterone groups received an injection of vehicle. On day 15 the test took place again, as described for day 1.

On day 1, both progesterone and Compound (1) had a stimulatory effect on proceptivity, compared to the vehicle group (**P<0.01, ANOVA followed by Dunnett's test). On day 15, a similar stimulatory effect was observed (**P<0.01, ANOVA followed by Dunnett's test) (see **Figure 3**). No significant difference was observed between the effects on day 1 and day 15 for each treatment group (paired t test). The effects of progesterone and Compound (1) were statistically similar. There were no changes in body weight or general behaviour between groups along the experiment.

From this study we can conclude that Compound (1) (15mg/kg, i.p.) has a stimulatory effect on proceptivity in the female rat, comparable to progesterone, and that such effect is unaffected by the repeated administration of the compound, which seems to be well tolerated.

Example 4

Effect of intracerebroventricular administration of Compound (1) on female rat sexual proceptivity

In order to elucidate the site of action for this effect we have administered the Compound (1) intracerebroventricularly (i.c.v.).

Ovariectomised female rats (Sprague Dawley, obtained from Charles River, UK) were stereotaxically implanted (coordinates 0.89mm behind Bregma, 1.3mm lateral and 2.5mm vertical) with stainless steel cannulae (6 mm long, O.D. 0.75mm), held in place with dental cement. Animals were housed in groups of three and returned to a reversed lighting system of 12h light:dark (lights off 5.00-17.00h).

Correct placement of the cannulae was assessed post-mortem. Rats were used for tests two weeks after ovariectomy (one week after cannulation). The experiments started at least 5h into the dark period. Forty eight hours before tests, the animals were primed with 5μg oestradiol benzoate (s.c, in corn oil) and adapted to the apparatus (in the absence of stimuli animals) for 10min on 2 consecutive days prior testing. The 10min test was carried out as previously described. The difference in the percentage of time spent investigating the male minus the female stimuli was calculated, out of the total time spent investigating stimuli.

Compound (**1**) was dissolved in 50% 2-hydroxypropyl-β-cyclodextrin in saline. It was administered i.c.v. over a 30sec period, with the aid of a pump set to deliver a flow of 10μl/min. The dosing volume was 5μl/rat. The compounds were administered 10min before tests. Progesterone (0.5mg/0.1ml) was dissolved in corn oil and administered subcutaneously (s.c.), 4h before test, as a positive control. As shown in **Figure 4**, Compound (**1**) dose-dependently (3-30μg/rat) increased the percentage of time spent investigating the male stimulus, with a MED of 10μg. The effect of this dose was similar to the effect of progesterone.

From this study we can conclude that the effect of Compound (**1**) on female sexual proceptivity is centrally mediated.

In figure 4 bars represent percentage of time spent investigating male, minus the percentage of time spent investigating the female stimuli±SEM, (n=7-8 per group). *P<0.05, **P<0.01 *vs* vehicle (Kruskal-Wallis ANOVA test followed by Mann-Whitney's test).

Example 5

Inhibitory effect of NMB on female rat sexual proceptivity and antagonism of this effect by Compound (1)

We have investigated the potentially inhibitory effect of the BB_1 agonist neuromedin B (NMB) on female rat sexual proceptivity.

5   Ovariectomised female rats (Sprague Dawley, obtained from Charles River, UK) were stereotaxically implanted (coordinates 0.89mm behind Bregma, 1.3mm lateral and 2.5mm vertical) with stainless steel cannulae (6 mm long, O.D. 0.75mm), held in place with dental cement. Animals were housed in groups of three and returned to a reversed lighting system of 12h light:dark (lights off 5.00-17.00h).
Correct placement of the cannulae was assessed post-mortem. Rats were used for tests

10   two weeks after ovariectomy (one week after cannulation). The experiments started at least 5h into the dark period. Forty eight hours before tests, the animals were primed with 5μg oestradiol benzoate (OB) (s.c, in corn oil) and adapted to the apparatus (in the absence of stimuli animals) for 10min on 2 consecutive days prior testing. The 10min test was carried out as previously described. The difference in the percentage

15   of time spent investigating male minus female was calculated, out of the total time spent investigating stimuli.

    Progesterone (Prog, 0.5mg/0.1ml) was dissolved in corn oil and administered subcutaneously (s.c.), 4h before test, to induce proceptive behaviour. Compound (1)

20   (15mg/kg, i.p.) was dissolved in 50% 2-hydroxypropyl-β-cyclodextrin in saline and administered 1h before the i.c.v. administration. Neuromedin B was obtained from Bachem, UK. It was dissolved in isotonic saline and administered i.c.v. over a 30sec period, with the aid of a pump set to deliver a flow of 10μl/min, 10min before tests.
The dosing volume was 5μl/rat. Each rat received a total amount of 100ng.

25

    As shown in **Figure 5**, progesterone (Prog) increased the percentage of time spent investigating the male stimulus, compared to the vehicle group, thus showing stimulation of proceptive behaviour. NMB (100ng, i.c.v.) significantly reduced proceptivity in progesterone-treated rats. Moreover, pre-treatment with Compound (1)

30   which acts as an antagonist (15mg/kg, i.p.) prevented the inhibitory effect of NMB.
However, the blockade obtained with the dose of Compound (1) used was not total.

From the present study we can conclude that stimulation of BB1 receptors with an agonist results in inhibition of proceptive behaviour. This inhibitory effect may be prevented by the presence of an antagonist. e.g. Compound (1) In figure 5 the bars represent percentage of time spent investigating male, minus the percentage of
5   time spent investigating the female stimuli±SEM, (n=8-12 per group). ***P<0.001 vs progesterone (One-way ANOVA followed by Dunnett's test).

Example 6

10   **Demonstration that the effect of Compound (1) on female sexual behaviour is not mediated through sexual hormones**

Previous examples have shown that Compound (1) (nanomolar affinity "mixed" BB_1/BB_2 receptor antagonist) has a dose-dependent stimulatory effect on
15   sexual activity in the female rat, both on proceptivity and receptivity. Although the animals used in that study were ovariectomised, and therefore steroid hormones release can not be expected to occur in response to the compound, there is a possibility that the adrenal glands might secrete steroid hormones in response to Compound (1). If that was the case, the mediation of the stimulatory effects by
20   progesterone would be relevant for rodents, but it would not be the case for primates. In the present study, we have investigated the potential effect of the bombesin receptor antagonist Compound (1) on secretion of progesterone. Oestradiol and pituitary hormones (Luteinising hormone (LH), follicle stimulating hormone (FSH) and prolactin) have also been analysed in the same animals.

25

Ovariectomised adult female Sprague Dawley rats (180-200g) were housed in groups of 6 in a reversed lighting system of 12h light:dark (lights off 7.00-19.00h). They were used for the experiments at least two weeks after ovariectomy. Forty eight hours before tests, the animals were primed with oestradiol benzoate (5µg/0.1ml in
30   corn oil, s.c.). Progesterone (0.5mg/0.1ml, in corn oil, s.c.) was administered 4h before blood collection, as a positive control. Compound (1) (3-10mg/kg, i.p.) was administered in 50% 2-hydroxypropyl-β-cyclodextrin, 1h prior to blood collection.

Blood was collected from the trunk, after decapitation. It was immediately centrifuged (3500r.p.m., 4°C, 5min) and the plasmas frozen until assayed for hormonal content, using commercially available radioimmunoassay kits (^{125}I-labelled hormones) for oestradiol, progesterone, LH, FSH and prolactin.

5

A single administration of progesterone resulted in a significant increase in the progesterone plasma levels (P<0.05), and a significant decrease in LH plasma levels (P<0.01), compared to animals injected with vehicle (Kruskal-Wallis followed by Mann-Whitney test). However, Compound (1) (3-10mg/kg, i.p.) had no effect on the

10 plasma levels of progesterone (**Figure 6**, where animals were pre-treated with 5μg oestradiol benzoate, s.c., 48h before the test. They were tested 1h or 4h post-injection of Compound (1) (3-10mg/kg, p.o.) or progesterone (0.5mg/0.1ml, s.c.) respectively. Values represent mean±SEM, (n=9 per group). *P<0.05, vs vehicle (Kruskal-Wallis followed by Mann-Whitney test, vs vehicle)), oestradiol (**Figure 7**, where animals

15 were pre-treated with 5μg oestradiol benzoate, s.c., 48h before the test. They were tested 1h or 4h post-injection of Compound (1) (3-10mg/kg, p.o.) or progesterone (0.5mg/0.1ml, s.c.) respectively. Values represent mean±SEM, (n=6-7 per group)), prolactin (**Figure 8,** where animals were pre-treated with 5μg oestradiol benzoate, s.c., 48h before the test. They were tested 1h or 4h post-injection of Compound (1) (3-

20 10mg/kg, p.o.) or progesterone (0.5mg/0.1ml, s.c.) respectively. Values represent mean±SEM, (n=10 per group)) LH (**Figure 9**, where animals were pre-treated with 5μg oestradiol benzoate, s.c., 48h before the test. They were tested 1h or 4h post-injection of Compound (1) (3-10mg/kg, p.o.) or progesterone (0.5mg/0.1ml, s.c.) respectively. Values represent mean±SEM, (n=10 per group). **P<0.01, vs vehicle

25 (Kruskal-Wallis followed by Mann-Whitney test, vs vehicle)) or FSH (**Figure 10,** where animals were pre-treated with 5μg oestradiol benzoate, s.c., 48h before the test. They were tested 1h or 4h post-injection of Compound (1) (3-10mg/kg, p.o.) or progesterone (0.5mg/0.1ml, s.c.) respectively. Values represent mean±SEM, (n=10 per group).

30

From this experiment we can conclude that Compound (1) did not have an effect on the secretion of sexual hormones, thus suggesting that the effects of the compound on female sexual activity must be mediated by different mechanisms, maybe involving neurotransmitters.

5

Example 7

Effect of Compound (1) on the sexual behaviour of normal male rats

10   The potentially stimulatory effect of Compound (1) on male sexual behaviour has been tested on sexually vigorous rats. Sprague Dawley male rats (Charles River, UK) were kept, 4 rats per cage, in a reversed lighting regime (12:12 hours, lights off at 5.00 h), with free access to food and water. The rats were pre-selected by being presented with a receptive female at 4 days intervals, i.e. every third day (having 2

15   clear days between presentations) until completing 6-7 days of baseline determination. The animals showing consistently vigorous behaviour (ejaculatory latencies <300s) were chosen for further experiments (n=24). Animals were randomised into three groups. All animals received all three treatments following a latin-square design. Treatments were administered once a week, with a baseline test in

20   between treatments (4 days intervals between baseline and test day). Treatments were Compound (1) (15mg/kg, dissolved in 50% 2-hydroxypropyl-β-cyclodextrin in saline), vehicle, or Fluoxetine (20mg/kg dissolved in 100% DMSO). All treatments were administered i.p. in a 1ml/kg volume, 1h before tests.

25   For all the sexual behaviour tests, the males were placed in an observation arena (50-60 cm diameter), starting 5 hours into the dark cycle and observed under red illumination. Three to 4 minutes after placing the male in the arena, a receptive female (ovariectomised, bearing a 7 mm Silastic implant of oestradiol benzoate) was introduced to the arena and the following parameters noted: Mount Latency: time (in

30   seconds) taken between introduction of female and first mount. A maximum time of 15 minutes (900 seconds) was allowed, and the test terminated if no mounts were recorded within that time (**Figure 11**), Intromission Latency: time (in seconds) taken

between introduction of female and first intromission (**Figure 12**), Number of Mounts: to reach ejaculation. When ejaculation was not reached, the number of mounts was not analyzed, Number of Intromissions: to reach ejaculation. When ejaculation was not reached, the number of intromissions was not analyzed (**Figure 13** is number of mounts + intromissions), Ejaculation Latency: time (in seconds) taken from first intromission to ejaculation. A maximum time of 30 minutes (1800 seconds) was given, and the test terminated if ejaculation was not achieved in that time (**Figure 14**), and Refractory Period: time (in seconds) taken from ejaculation to the first mount of the next series of sexual activity. In those animals reaching ejaculation the test was terminated at the end of the refractory period, as indicated by the first mount of the next sexual cycle (**Figure 15**).

A one-way ANOVA followed by Dunnett's t test was used to compare treated vs vehicle groups each day of testing, for all the sexual behaviour parameters. (*$P<0.05$, **$P<0.01$; n=15-16).

Mount latency and intromission latency were significantly increased in the fluoxetine-treated group compared to the vehicle group. Ejaculation latency and refractory period were also increased in this group, showing a decrease in sexual performance as well as the decreased arousal. No changes were seen in the number of mounts and intromissions required to achieve ejaculation. Unlike Fluoxetine, Compound (**1**) had no effect on any of the parameters studied, at a dose shown to be stimulatory in sexually dysfunctional males (see example 9). From the present study we can conclude that Compound (**1**) has no effect on sexual behaviour in sexually vigorous males.

Example 8

Effect of Compound (1) on the sexual behaviour of sexually dysfunctional male rats

Fluoxetine induces ejaculation delay, anorgasmy and loss of sexual desire in humans (Crenshaw and Goldberg, 1996). A model of male sexual dysfunction in the rat, induced by daily administration of fluoxetine until a significant detrimental effect on sexual behaviour (arousal and ejaculation) was established. The potentially stimulatory effect of Compound (1) on male sexual behaviour in these sexually dysfunctional male rats was examined. The effects of Compound (1) were compared to those of yohimbine. Preclinical and clinical studies suggest that yohimbine may be an effective treatment for sexual side-effects caused SSRI (Hollander, E., McCarley, A. (1993) *J. Clin. Psychiatry* 53:207-209. and Jacobsen).

Sprague Dawley male rats (Charles River, UK) were kept, 4 rats per cage, in a reversed lighting regime (12:12 hours, lights off at 5.00 h), with free access to food and water. The rats were pre-selected by being presented with a receptive female at 4 days intervals, i.e. every third day (having 2 clear days between presentations) until completing 6-7 trials of baseline determination. The animals showing consistently vigorous behaviour (ejaculatory latencies <300s) were chosen for further experiments. Animals were treated for 3 consecutive days with either vehicle (water) or fluoxetine (20mg/kg, i.p., in a 2ml/kg dosing volume). On the fourth day, the animals treated with water received vehicle (veh+veh) and the animals treated with fluoxetine received one of the three following treatments: Compound (1) (15mg/kg, dissolved in 50% 2-hydroxypropyl-β-cyclodextrin in saline), vehicle (cyclodextrine), or yohimbine (2mg/kg dissolved in water). All treatments were administered i.p. in a 1ml/kg volume, 1h before tests.

For all the sexual behaviour tests, the males were placed in an observation arena (50-60 cm diameter), starting 5 hours into the dark cycle and observed under red illumination. Three to 4 minutes after placing the male in the arena, a receptive female (ovariectomised, bearing a 7 mm Silastic implant of oestradiol benzoate) was introduced to the arena and the following parameters noted: Mount Latency: time (in seconds) taken between introduction of female and first mount. A maximum time of 15 minutes (900 seconds) was allowed, and the test terminated if no mounts were recorded within that time (**Figure 16**), Ejaculation Latency: time (in seconds) taken

from first intromission to ejaculation. A maximum time of 30 minutes (1800 seconds) was given, and the test terminated if ejaculation was not achieved in that time (**Figure 17**), Percentage of males achieving ejaculation within 30 minutes was calculated (**Figure 18**).

5

A one-way ANOVA followed by Dunnett's t test was used to compare the fluoxetine+vehicle group and other groups for mount and ejaculatory latencies. Percentage of animals ejaculating was analysed using a Chi-square test followed by Fisher's test. (*: P<0.05, **: P<0.01, ***: P<0.001; n=15-19).

10

Mount latency and ejaculation latency were significantly increased in the fluoxetine-treated groups compared to the vehicle+vehicle group, indicating a decrease in sexual desire as well as sexual performance in these groups. The number of animals ejaculating was significantly lower in the fluoxetine-treated groups,

15 indicating anorgasmy. Compound (**1**) significantly decreased the mount and ejaculatory latencies at the same time as increasing the percentage of animals ejaculating in the animals rendered sexually dysfunctional by the fluoxetine treatment, to levels comparable to normal animals (veh+veh). Yohimbine followed a similar trend, although this did not reach significance.
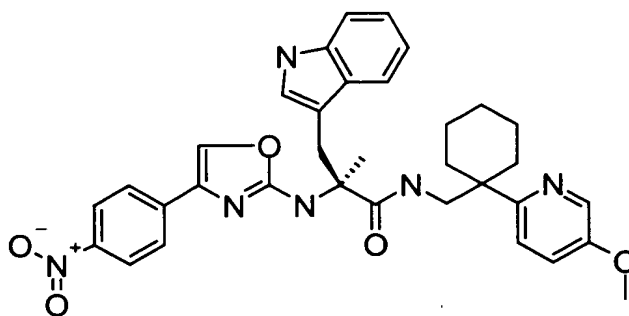
20 From the present study we can conclude a stimulatory effect of Compound (**1**) on sexual behaviour in males suffering from sexual dysfunction, at the level of sexual desire, sexual performance and anorgasmy.

Example 9

25

(S)-3-(1*H*-Indol-3-yl)-*N*-[1-(5-methoxy-pyridin-2-yl)-cyclohexylmethyl]-2-methyl-2-[4-(4-nitro-phenyl)-oxazol-2-ylamino]-propionamide

1.   To a stirred solution of p-nitrophenylchloroformate (9.27g, 46mmol) in THF (200ml) at 0°C was added dropwise a solution of H-(S)-αMeTrp-OMe (**1a**) (10.7g, 46 mmol) and triethylamine (6.4ml, 46mmol) in THF (100ml) over 1 hour. Stirring was continued for a further 30 minutes at room temperature, after which aqueous ammonia (15ml) was added. IR after 10 minutes indicated bands at 1732 and 1660 cm⁻¹. The THF was removed under reduced pressure, and the residue was taken up in EtOAc and washed with 1N HCl (x2), Na_2CO_3 solution (until intense yellow colour subsided, ~x8), brine, and dried ($MgSO_4$). The solvent was removed under reduced pressure to give **2a** as a foam (10.3g, 82%):MS m/e (AP+): 276.16 (M⁺ + H, 100%);

MS m/e (AP-): 274.11 (M⁻ - H, 100%);

IR (film): 3383, 1724, 1657, 1600, 1539, 1456, 1374, 1256, 1108, 743 cm⁻¹;

¹H NMR (CDCl₃): δ= 1.70 (3H, s), 3.38 (1H, d, J=14.7 Hz), 3.59 (1H, d, J=14.7 Hz), 3.71 (3H, s), 4.22 (2H, s), 5.16 (1H, s), 6.99 (1H, d, J=2.2 Hz), 7.08-7.20 (2H, m), 7.34 (1H, d, J=8.1 Hz), 7.59 (1H, d, J=7.8 Hz), 8.09 (1H, s).

2.   The urea (**2a**) (6.4g, 23mmol) and 2-bromo-1-(4-nitro-phenyl)-ethanone (6.0g, 23mmol) were stirred in toluene (500ml)/dioxan (100ml) and maintained under reflux for 30 hours, after which solvent was removed under reduced pressure and the residue was purified by chromatography using a 90g Biotage cartridge. 10% EtOAc in heptane eluted the bromide starting material. 20% EtOAc eluted the desired product. Removal of solvent under reduced pressure gave **3a** as a foam (840mg, 9%):

MS m/e (ES+): 420.56 (M⁺, 100%);

IR (film): 3394, 1732, 1632, 1605, 1574, 1515, 1456, 1334, 1253, 1210, 1108, 1072, 940, 854, 734 cm^{-1};

^{1}H NMR (CDCl$_3$): δ= 1.91 (3H, s), 3.46 (1H, d, J=14.6 Hz), 3.69 (3H, s), 3.78 (1H, d, J=14.6 Hz), 5.57 (1H, s), 6.89 (1H, d, J=2.2 Hz), 7.03-7.08 (1H, m), 7.14-7.18 (1H, m), 7.34 (1H, d, J=8.1 Hz), 7.41 (1H, d, J=8.1 Hz), 7.63 (1H, s), 7.85 (2H, d, J=9.0 Hz), 8.05 (1H, s), 8.24 (2H, d, J=8.6 Hz).

3.   The ester (**3a**) (840mg, 2mmol) was dissolved in dioxan (50ml) and LiOH.H$_2$0 (336mg, 8mmol) in H$_2$O (25ml) was added. The mixture was stirred vigorously overnight, and then neutralised with 1M HCl (8ml, 8mmol). The majority of the dioxan was removed under reduced pressure and the product was crystallised, filtered off, washed with water and dried under reduced pressure to give pure **4a** (668mg, 82%):

MS m/e (ES+): 407 (M$^+$ + H);

IR (film): 1633 cm^{-1};

^{1}H NMR (DMSO-d$_6$) δ= 1.49 (3H, s), 3.30-3.35 (1H, m, masked by H$_2$0), 3.59 (1H, d, J=14.7 Hz), 6.86-6.90 (1H, m), 6.99-7.03 (2H, m), 7.30-7.36 (2H, m), 7.48 (1H, s), 7.94 (2H, d, J=9.0 Hz), 8.27-8.30 (3H, m), 10.88 (1H, s), (*CO$_2$H not seen*).

4.   The acid (**4a**) (1.148g, 2.8mmol), *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HBTU, 1.06g, 2.8mmol), and *N,N*-diisopropylethylamine (DIPEA, 490μl, 2.8mmol) were stirred in DMF (10ml) for 5 minutes before adding DIPEA (490μl, 2.8mmol) and [1-(5-methoxy-2-pyridyl)cyclohexyl]-methanamine (see WO 98/07718, 678mg, 3.1mmol). HPLC indicated that reaction was complete within 1 hour. Solvent was removed under reduced pressure and the residue was taken up in EtOAc. The organic layer was washed with brine, saturated NaHCO$_3$ (x3), brine and dried (MgSO$_4$), after which solvent was removed under reduced pressure. The residue was purified by chromatography using RP silica with 65% MeOH in H$_2$O. Pure fractions were evaporated to give the desired product as an amorphous solid (1.12g, 66%):

MPt: 100-105°C;

MS m/e (ES+): 609.63 (M$^+$ + H, 100%);

IR (film): 3359, 3272, 3054, 2932, 2857, 1628, 1606, 1573, 1515, 1488, 1393, 1336, 1268, 1232, 1181, 1150, 1131, 1097, 1028, 1012, 962, 939, 900, 853, 831, 737 cm^{-1};

^{1}H NMR (CDCl$_3$): δ= 1.10-1.60 (8H, m), 1.72 (3H, s), 1.95-2.02 (2H, m), 3.31-3.42 (2H, m), 3.41 (1H, d, J=14.6 Hz), 3.50 (1H, d, J=14.6 Hz), 3.69 (3H, s), 5.34 (1H, s), 6.90-6.97 (2H, m), 7.04-7.09 (2H, m,) 7.14-7.19 (1H, m), 7.33 (1H, d, J=8.1 Hz), 7.46 (1H, d, J=7.8 Hz), 7.54 (1H, s), 7.77 (2H, d, J=8.8 Hz), 8.00 (1H, d, J=2.9 Hz), 8.04 (1H, s), 8.21 (2H, d, J=8.8 Hz); *(amide masked by CHCl$_3$)*
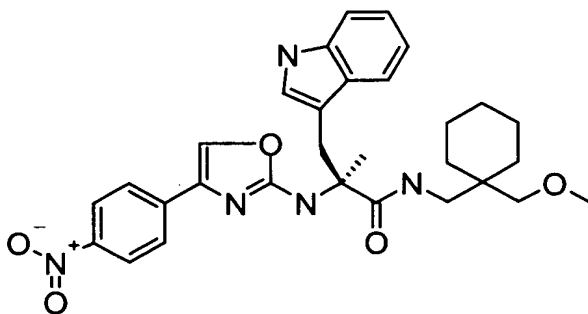
HPLC A: Rt. 11.86 min, 99.8/100% purity, 20-100% CH$_3$CN in H$_2$O (+0.1%TFA) over 15 min at 1ml min^{-1}, Prodigy ODSIII 250x4.6mm 5µM, 215 and 254 nm;

HPLC B: Rt. 14.32 min, 100/100% purity, 80:20 methanol/Tris buffer at pH9, 1mlmin^{-1}, Prodigy ODSIII 250x4.6mm 5µM, 215 and 254 nm.

Example 10

(S)-3-(1*H*-Indol-3-yl)-*N*-(1-methoxymethyl-cyclohexylmethyl)-2-methyl-2-[4-(4-nitro-phenyl)-oxazol-2-ylamino]-propionamide

The above compound was synthesized from Intermediate 4a and Intermediate 13 using the same method as used for **Example 9**. The acid (**4a**) (203mg, 0.5mmol), HBTU (190mg, 0.5mmol), and DIPEA (87μl, 0.5mmol) were stirred in DMF (10ml) for 5 minutes before adding DIPEA (87μl x 2, 1.0mmol) and **Intermediate 13** (94mg, 0.5mmol, Scheme 6). After 4 hours the solvent was removed under reduced pressure and residue taken up in EtOAc. The organic layer was washed with brine, saturated $NaHCO_3$ (x3), brine, dried ($MgSO_4$) and solvent removed under reduced pressure. The residue was heated to 60°C in methanol and product filtered off. Drying under reduced pressure gave the desired product as a yellow crystalline solid (214mg, 78%):

MPt: 189-192°C;

MS m/e (ES+): 546.49 (M^+ + H, 100%);

IR (film): 3285, 2928, 2849, 1637, 1604, 1516, 1453, 1334, 1260, 1108, 1077, 860, 743, 729 cm^{-1};

^{1}H NMR (DMSO-d_6): δ= 1.10-1.35 (10H, m), 1.44 (3H, s), 2.91-3.01 (3H, m), 3.06-3.12 (1H, m), 3.07 (3H, s), 3.26-3.31 (1H, m), 3.64 (1H, d, J=14.4 Hz), 6.87-6.93 (2H, m), 7.01 (1H, t, J=7.4 Hz), 7.29-7.37 (3H, m), 7.44 (1H, s), 7.94 (2H, d, J=9.0 Hz), 8.26 (2H, d, J=8.8 Hz), 8.34 (1H, s), 10.84 (1H, s);

HPLC A: Rt. 17.07 min, 100/100% purity, 20-100% CH_3CN in H_2O (+0.1%TFA) over 15 min at 1mlmin^{-1}, Prodigy ODSIII 250x4.6mm 5μM, 215 and 254 nm;

HPLC B: Rt. 14.35 min, 100/100% purity, 80:20 methanol/Tris buffer at pH9, 1mlmin^{-1}, Prodigy ODSIII 250x4.6mm 5μM, 215 and 254 nm.

Example 11

(S)-3-(1H-Indol-3-yl)-2-methyl-2-[4-(4-nitro-phenyl)-oxazol-2-ylamino]-N-(2-oxo-2-phenyl-ethyl)-propionamide.
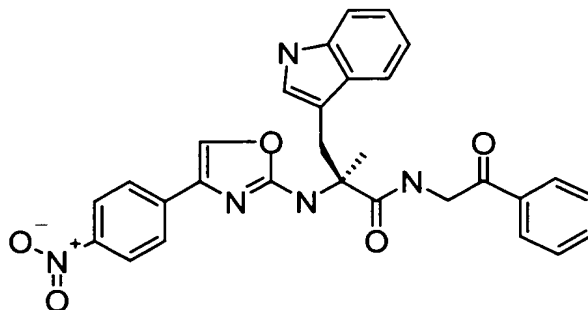
The above compound was synthesised from **Intermediate 4a** using the same method as used for **Example 9**. The acid (**4a**) (203mg, 0.5mmol), HBTU (190mg, 0.5mmol), and DIPEA (87μl, 0.5mmol) were stirred in DMF (10ml) for 5 minutes before adding DIPEA (87μl, 0.5mmol) and 2-amino-1-phenyl-ethanone (103mg, 0.6mmol). After 4 hours the solvent was removed under reduced pressure and residue taken up in EtOAc, washed with brine, saturated NaHCO₃ (x3), brine, dried (MgSO₄) and solvent removed under reduced pressure. The residue was purified by chromatography using NP 20g Mega Bond Elut cartridge and 40% ethyl acetate in heptane as eluent. Evaporation of pure fractions gave the desired product as a yellow amorphous solid (170mg, 65%):

MPt: 80-90°C;

MS m/e (AP+): 525.83 (16%), 524.44 (M⁺ + H, 100%);

IR (film): 3396, 3059, 2983, 2932, 1694, 1628, 1605, 1575, 1514, 1449, 1336, 1284, 1264, 1225, 1181, 1154, 1096, 1072, 1010, 1001, 940, 853, 737 cm⁻¹;

¹H NMR (DMSO-d₆): δ= 1.50 (3H, s), 3.39 (1H, d, J=14.7 Hz), 3.64 (1H, d, J=14.6 Hz), 4.53 (1H, d.d, J=18.1 and 5.4 Hz), 4.66 (1H, d.d, J=18.1 and 5.5 Hz), 6.87 (1H, t, J=7.4 Hz), 6.95 (1H, d, J=2.2 Hz), 7.00 (1H, t, J=7.4 Hz), 7.30 (1H, d, J=8.1 Hz), 7.34 (1H, d, J=8.1 Hz), 7.41 (1H, s), 7.50-7.55 (2H, m), 7.62-7.67 (1H,m), 7.94-7.99 (4H, m), 8.24 (1H, t, J=5.4 Hz), 8.27 (2H, d, J=9.0 Hz), 8.31 (1H, s), 10.86 (1H, s);
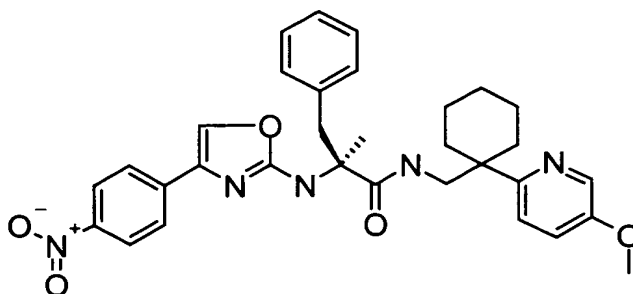
HPLC A: Rt. 20.83 min, 98.3/99.6% purity, 20-100% CH₃CN in H₂O (+0.1%TFA) over 25 min at 1mlmin⁻¹, Prodigy ODSIII 250x4.6mm 5μM, 215 and 254 nm;

HPLC B: Rt. 6.82 min, 100/100% purity, 80:20 methanol/Tris buffer at pH9, 1mlmin⁻¹, Prodigy ODSIII 250x4.6mm 5µM, 215 and 254 nm.

Example 12

(S)-N-[1-(5-Methoxy-pyridin-2-yl)-cyclohexylmethyl]-2-methyl-2-[4-(4-nitro-phenyl)-oxazol-2-ylamino]-3-phenyl-propionamide

The above compound was synthesised from **1b** and **4b** using the same methods as used for **Example 9**. The acid (**4b**) (120mg, 0.33mmol), HBTU (124mg, 0.33mmol), and DIPEA (114µl, 0.66mmol), and [1-(5-methoxy-2-pyridyl)cyclohexyl]-methanamine[1] (86mg, 0.4mmol) were stirred in DMF (4ml) for 18 hours. Solvent removed under reduced pressure and residue taken up in EtOAc. The organic layer was washed with brine, saturated NaHCO₃ (x3), brine, dried (MgSO₄) and solvent removed under reduced pressure. The residue was purified by chromatography using NP silica with 10-80% ethyl acetate in heptane. Pure fractions were evaporated to give the desired compound as a yellow amorphous solid (90mg, 49%):

MS m/e (AP+): 570.23 ($M^+ + H$, 100%);

IR (film): 3363, 2930, 2856, 1658, 1651, 1628, 1574, 1515, 1488, 1334, 1268, 1232, 1073, 1030, 938, 852 cm⁻¹;

¹H NMR (DMSO-d₆): δ= 0.94-1.46 (11H, m), 1.98-2.10 (2H, m), 3.04-3.14 (2H, m), 3.25-3.32 (1H, m), 3.57 (1H, d, J=13.6 Hz), 3.73 (3H, s), 6.95-7.00 (3H, m), 7.10-7.24 (5H, m), 7.44 (1H, s), 7.93 (2H, d, J=8.8 Hz), 8.14 (1H, d, J=2.8 Hz), 8.27 (2H, d, J=9.2 Hz), 8.36 (1H, s);
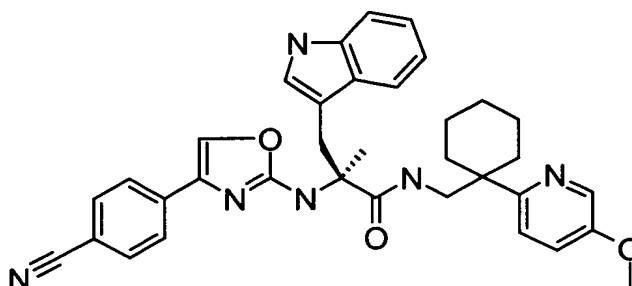
HPLC A: Rt. 5.49 min, 99.76% purity, 20-100% CH$_3$CN in H$_2$O (+0.1%TFA) over 7 min at 1.5 mlmin^{-1}, Prodigy ODSIII 150x4.6mm 3µM at 40°C, 200-300 nm;

HPLC B: Rt. 5.72 min, 99.46% purity, 20-90% CH$_3$CN/Tris (1mM) over 7 min at 2mlmin^{-1}, Prodigy Phenyl-Ethyl, 100x4.6mm 5µM at 30°C, 200-300 nm.

Example 13

(S)-2-[4-(4-Cyano-phenyl)-oxazol-2-ylamino]-3-(1*H*-indol-3-yl)-*N*-[1-(5-methoxy-pyridin-2-yl)-cyclohexylmethyl]-2-methyl-propionamide

The above compound was synthesized from **2a** via **6a** as outlined in Scheme 2 using methods analogous to those used for **Example 9**. The acid **(6a)** (309mg, 0.8mmol), HBTU (303mg, 0.8mmol), DIPEA (140µl, 0.8mmol) were stirred in DMF (5ml) for 5 minutes before adding DIPEA (140µl, 0.8mmol) and [1-(5-methoxy-2-pyridyl)cyclohexyl]-methanamine (WO 98/07718) (185mg, 0.84mmol). HPLC indicated reaction complete within 1 hour. Solvent removed under reduced pressure and residue taken up in EtOAc. Washed with brine, saturated NaHCO$_3$ (x3), brine, dried (MgSO$_4$) and solvent removed under reduced pressure. Residue purified by chromatography using RP silica with 65% MeOH in H$_2$O. Pure fractions were evaporated to give **Example 13** as a white amorphous solid (320mg, 68%):

MPt: 105-108°C;

MS m/e (ES+): 589.32 (M$^+$ + H, 100%), 590.18 (62%);

IR (film): 3355, 2932, 2857, 2225, 1628, 1572, 1521, 1489, 1456, 1328, 1269, 1232, 1096, 1072, 1029, 938, 844, 741 cm^{-1};

^{1}H NMR (CDCl$_3$): δ= 1.20-1.60 (8H, m), 1.70 (3H, s), 1.93-2.03 (2H, m), 3.30-3.52 (4H, m), 3.68 (3H, s), 5.30 (1H, s), 6.89 (1H, d, J=2.4 Hz), 6.94 (1H, d.d, J=8.8 and 2.9 Hz), 7.03-7.09 (2H, m,) 7.14-7.19 (1H, m), 7.20-7.25 (1H, m), 7.33 (1H, d, J=8.1 Hz), 7.46 (1H, d, J=7.8 Hz), 7.50 (1H, s), 7.63 (2H, d, J=8.5 Hz), 7.72

5   (2H, d, J=8.3 Hz); 8.00 (1H, d, J=2.9 Hz), 8.05 (1H, s);

HPLC A: Rt. 11.63 min, 97.7/100% purity, 20-100% CH$_3$CN in H$_2$O (+0.1%TFA) over 15 min at 1mlmin^{-1}, Prodigy ODSIII 250x4.6mm 5μM, 215 and 254 nm;

HPLC B: Rt. 9.20 min, 100/100% purity, 80:20 methanol/Tris buffer at pH9,

10   1mlmin^{-1}, Prodigy ODSIII 250x4.6mm 5μM, 215 and 254 nm.

Example 14

(S)-3-(1*H*-Indol-3-yl)-*N*-[1-(5-methoxy-pyridin-2-yl)-cyclohexylmethyl]-2-methyl-

15   2-(4-phenyl-oxazol-2-ylamino)-propionamide
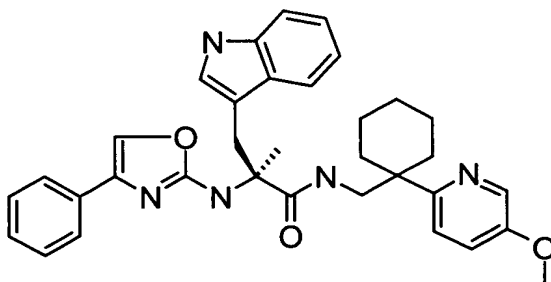
The above compound was synthesised from **2a** via **6b** as outlined in Scheme 2 using methods analogous to those used for **Example 9**. The acid (**6b**) (57mg,

20   0.148mmol), HBTU (56mg, 0.148mmol), DIPEA (26μl, 0.148mmol) were stirred in DMF (5ml) for 5 minutes before adding DIPEA (26μl, 0.148mmol) and [1-(5-methoxy-2-pyridyl)cyclohexyl]-methanamine (see WO 98/07718, 34mg, 0.148mmol). HPLC indicated that the reaction was complete within 2 hours. Solvent was removed under reduced pressure and the residue was taken up in EtOAc, washed with brine,

25   sat. NaHCO$_3$ (x3), brine, dried (MgSO$_4$) and solvent removed under reduced pressure. The residue was purified by chromatography using RP silica with 70% MeOH in H$_2$O

as eluent. Repurification using NP 8g Biotage cartridge with 45% ethyl acetate in heptane as eluent gave the desired product as a glass (20mg, 24%):

MPt: 85-90°C;

MS m/e (ES+): 564.06 (M⁺, 87%), 564.96 (M⁺+ H, 100%);

5   IR (film): 3289, 2931, 2857, 1627, 1569, 1520, 1488, 1456, 1337, 1267, 1233, 1072, 1072, 1030, 939, 739 cm⁻¹;

^{1}H NMR (DMSO-d₆): δ= 0.95-1.45 (11H, m), 2.00-2.10 (2H, m), 3.10-3.25 (2H, m), 3.21 (1H, d, J=14.6 Hz), 3.59 (1H, d, J=14.6 Hz), 3.71 (3H, s), 6.84-7.14 (7H, m), 7.24-7.40 (5H, m,), 7.70 (2H, d, J=7.6 Hz), 8.05 (1H, s), 8.15 (1H, d, J=2.9

10   Hz), 10.82 (1H, s);

HPLC A: Rt. 12.01 min, 96.8/95.3% purity, 20-100% CH₃CN in H₂O (+0.1%TFA) over 15 min at 1mlmin⁻¹, Prodigy ODSIII 250x4.6mm 5µM, 215 and 254 nm;

HPLC B: Rt. 17.27 min, 100/100% purity, 80:20 methanol/Tris buffer at pH9,

15   1mlmin⁻¹, Prodigy ODSIII 250x4.6mm 5µM, 215 and 254 nm.

Example 15

20   **(S)-2-(4-Ethyl-oxazol-2-ylamino)-3-(1H-indol-3-yl)-N-[1-(5-methoxy-pyridin-2-yl)-cyclohexylmethyl]-2-methyl-propionamide**
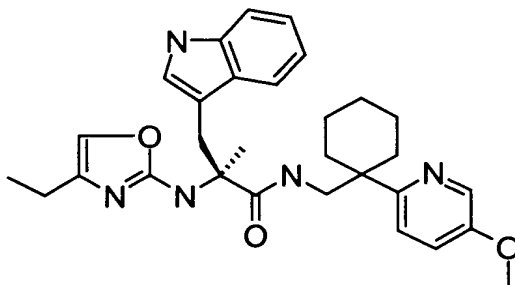
The above compound was synthesized from **2a** via **6c** as outlined in Scheme 2 using methods analogous to those used for **Example 9**. The acid (**6c**) (188mg, 0.6mmol), HBTU (228mg, 0.6mmol), and DIPEA (105µl, 0.6mmol) were stirred in DMF (10ml) for 5 minutes before adding DIPEA (105µl, 0.6mmol) and [1-(5-

25   methoxy-2-pyridyl)cyclohexyl]-methanamine (see WO 98/07718, 150mg, 0.65mmol). HPLC indicated that the reaction was complete within 4 hours. Solvent

was removed under reduced pressure and residue was taken up in EtOAc, washed with brine, sat. NaHCO₃ (x3), brine, dried (MgSO₄) and solvent removed under reduced pressure. The residue was purified by chromatography using RP silica with 65% MeOH in H₂O. The product was repurified using 20g Mega Bond Elut silica cartridge with 45% ethyl acetate in heptane as eluent. Pure fractions were evaporated to give the above compound as a glass (30mg, 10%):

MPt: 60-65°C;

MS m/e (ES+): 516.24 (M^+ + H, 47%), 517.01 (100%), 538.10 (M^+ + Na, 25%);

IR (film): 3272, 3054, 2931, 2856, 1651, 1622, 1596, 1573, 1520, 1489, 1457, 1358, 1268, 1232, 1206, 1131, 1083, 1028, 949, 830, 740 cm⁻¹;

¹H NMR (DMSO-d₆): δ= 1.10-1.50 (8H, m), 1.11 (3H, t, J=7.4 Hz), 1.29 (3H, s), 2.05-2.15 (2H, m), 2.28-2.34 (2H, m), 3.08-3.18 (3H, m), 3.48 (1H, d, J=14.4 Hz), 3.79 (3H, s), 6.80-6.90 (3H, m), 6.97-7.04 (2H, m,), 7.10-7.20 (3H, m), 7.27-7.30 (2H, m), 8.17 (1H, d, J=2.9 Hz), 10.80 (1H, s);

LCMS: Rt. 1.36 min, 100% purity, 5-100% CH₃CN in H₂O (+0.1% Formic acid) over 2 min at 4 mlmin⁻¹, Prodigy ODSIII 50x4.6mm 5μM, 215 nm, MS m/e (ES+) 515.95 (100%);

HPLC B: Rt. 12.29 min, 100/100% purity, 80:20 methanol/Tris buffer at pH9, 1 mlmin⁻¹, Prodigy ODSIII 250x4.6mm 5μM, 215 and 254 nm;

Example 16

(S)-3-(1H-Indol-3-yl)-N-[1-(5-methoxy-pyridin-2-yl)-cyclohexylmethyl]-2-methyl-2-[4-(4-nitro-phenyl)-thiazol-2-ylamino]-propionamide
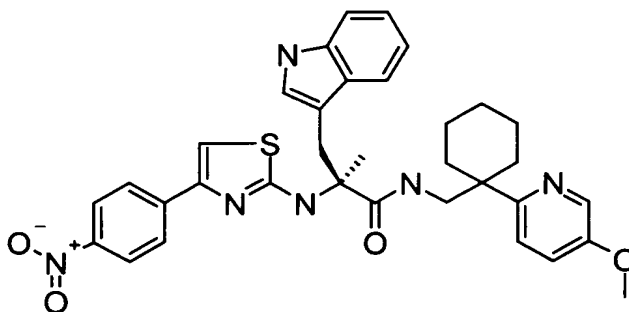
The above compound was synthesized using a one-pot procedure as outlined in Scheme 3. A suspension of H-S-αMeTrp-OH (**Intermediate 7**) (437mg, 2mmol), 2-chloro-4-(4-nitro-phenyl)-thiazole (see Peet, Norton P.; Sunder, Shyam. Reinvestigation of the reported preparation of 3-(4-nitrophenyl)thiazolo[2,3-c][1,2,4]triazepines, *J. Heterocycl. Chem.* (1986), 23(2), 593-5; 481mg, 2mmol), copper (I) iodide (38mg, 0.2mmol), and K_2CO_3 (415mg, 3mmol) in DMF (12ml) under nitrogen was heated to 130°C for 12 hours. The reaction mixture was cooled to ambient temperature before adding HBTU (759mg, 2mmol) and [1-(5-methoxy-2-pyridyl)cyclohexyl]-methanamine (see WO 98/07718; 441mg, 2mmol). The mixture was stirred overnight, then concentrated in vacuo, after which the residue was partitioned between water (20ml) and dichloromethane (30ml). The organic phase was separated and filtered through silica (3x12cm) using 500ml of dichloromethane and then 500ml of dichloromethane-ether (1:1). Fractions containing product were concentrated under reduced pressure. The residue was absorbed onto 3.5g silica and purified by chromatography (3x11cm) using heptane-ethyl acetate (1:1.1). The product was repurified using RP chromatography (Biotage KP-C18-HS Flash 12M, 15ml.min⁻¹, 60-100% methanol in water). Concentration under reduced pressure gave the desired compound as a pale yellow amorphous solid (27mg, 2%):

MPt: 110-114°C;

MS m/e (AP+): 624.88 (M^+, 100%), 625.70 ($M^+ + H$, 52%);

IR (film): 3385, 3279, 2931, 2855, 1654, 1595, 1542, 1509, 1456, 1341, 1268, 1231, 1108, 1058, 908, 844, 731 cm⁻¹;

¹H NMR (CDCl₃): δ= 1.15-1.55 (8H, m), 1.71 (3H, s), 1.90-2.00 (2H, m), 3.16-3.42 (2H, m), 3.46 (1H, d, J=14.9 Hz), 3.60 (1H, d, J=14.6 Hz), 3.70 (3H, s), 5.51 (1H, s), 6.89-6.93 (3H, m), 6.98 (1H, d, J=8.8 Hz), 7.05-7.10 (1H, m), 7.15-7.25 (2H, m), 7.34 (1H, d, J=8.3 Hz), 7.47 (1H, d, J=7.8 Hz), 7.90 (2H, d, J=9.0 Hz), 7.98 (1H, d, J=2.9 Hz), 9.05 (1H, s), 8.21 (2H, d, J=8.8 Hz);
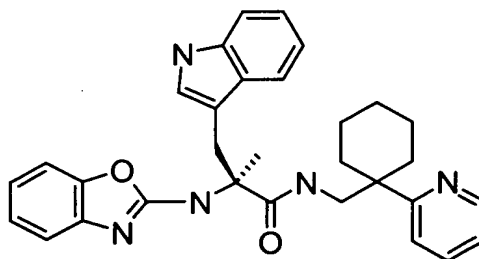
HPLC A: Rt. 12.30min, 99.4% purity, 20-100% CH₃CN in H₂O (+0.1%TFA) over 15 min at 1mlmin⁻¹, Prodigy ODSIII 250x4.6mm 5μM, 200-300 nm;

HPLC B: Rt. 15.38min, 99.5% purity, 80:20 methanol/Tris buffer at pH9, 1mlmin⁻¹, Prodigy ODSIII 250x4.6mm 5μM, 200-300 nm.

Example 17

(S)-2-(Benzooxazol-2-ylamino)-3-(1*H***-indol-3-yl)-2-methyl-***N***-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide**

5

1.   The following reagents were combined in the order that they are listed: **Intermediate 7** (545mg, 2.5mmol), 2-chlorobenzoxazole (384mg, 2.5mmol), potassium carbonate (346mg, 2.5mmol), benzyltriethylammonium chloride (TEBA,

10   114mg, 0.5mmol), triethylamine (1.04ml, 7.5mmol), DMF (12.5ml), deoxygenated water (1.25ml), copper (I) iodide (24mg, 0.125mmol), trans-dichlorobis(tri-*o*-tolyl-phosphine)palladium(II) (99mg, 0.125mmol). After heating at 100°C under nitrogen for 24 hours the DMF was removed under reduced pressure. The residue was taken up in ethyl acetate/water and the aqueous phase was acidified to pH 6-6.5 using citric

15   acid. The aqueous phase was extracted with three further portions of ethyl acetate. The combined organic layers were dried ($MgSO_4$) and solvent was removed under reduced pressure. The residue was purified by chromatography using 10g NP silica with 0-100% ethyl acetate in heptane. Crystallisation from dichloromethane gave (S)-2-(benzooxazol-2-ylamino)-3-(1*H*-indol-3-yl)-2-methyl-propionic   acid   (245mg,

20   29%). MS m/e (ES+) 335.97 (M^+ + H, 100%), 336.69 (85%).

2.   The propionic acid (234mg, 0.7mmol), HBTU (265mg, 0.7mmol), and DIPEA (122μl, 0.7mmol) were stirred in DMF (10ml) for 5 minutes before adding DIPEA (122μl, 0.7mmol) and   [1-(2- pyridyl)cyclohexyl]methylamine (WO   98/07718;

25   140mg, 0.74mmol). After 4 hours at ambient temperature the solvent was removed under reduced pressure. The residue was purified by chromatography using NP silica

with 50% ethyl acetate in heptane as eluent. Pure fractions were evaporated to give the desired compound as fine needles (44mg, 3%):

MPt: 198-200°C;

MS m/e (ES$^+$): 508.59 (100%, M$^+$ + H), 509.92 (10%);

IR (film): 3381, 3222, 3048, 2929, 2856, 1635, 1581, 1552, 1519, 1458, 1353, 1241, 1096, 742 cm^{-1};

^{1}H NMR (CDCl$_3$): δ = 1.20–1.60 (8H, m), 1.76 (3H, s), 1.95–2.05 (2H, m), 3.34 (1H, d.d, J=13.2 and 4.9 Hz), 3.45 (1H, d.d, J=13.2 and 5.6 Hz), 3.50 (2H, s), 5.67 (1H, s), 6.78–6.82 (1H, m), 6.89 (1H, d, J=2.2 Hz), 6.99-7.35 (10H, m), 7.43 (1H, d, J=8.1 Hz), 8.01 (1H, s), 8.24 (1H, d, J=4.6 Hz);

HPLC A: Rt. 10.54 min, 100/100% purity, 20-100% CH$_3$CN in H$_2$O (+0.1%TFA) over 15 min at 1mlmin^{-1}, Prodigy ODSIII 250x4.6mm 5μM, 215 and 254 nm;

HPLC B: Rt. 10.67 min, 100/100% purity, 80:20 methanol/Tris buffer at pH9, 1mlmin^{-1}, Prodigy ODSIII 250x4.6mm 5μM, 215 and 254 nm;

Example 18

(S)-3-(1*H*-Indol-3-yl)-2-methyl-2-(pyridin-4-ylamino)-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide
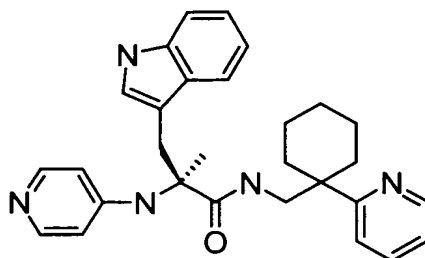
5   The above compound was prepared on the same scale and using an analogous method as used for **Example 17**.

1.   The method of **Example 17** was repeated except that 4-bromopyridine hydrochloride (486mg, 2.5mmol) was used.

10

2.   The acid from step 1 (30mg, 0.1mmol), HBTU (38mg, 0.1mmol), and DIPEA (18µl, 0.1mmol) were stirred in DMF (10ml) for 5 minutes before adding DIPEA (18µl, 0.1mmol) and [1-(2- pyridyl)cyclohexyl]methylamine (WO 98/07718; 19mg, 0.1mmol). After 2 hours at ambient temperature the solvent was removed under

15   reduced pressure. The residue was taken up in ethyl acetate and washed with sodium bicarbonate solution (x2), brine, and dried (MgSO$_4$). The solvent was removed under reduced pressure. The crude product was purified by chromatography using 10g ISCO Redisep cartridge with ethyl acetate as eluent. Repurification using 20g RP-C18 with 70% methanol in water and subsequent evaporation gave the desired product in

20   crystalline form (6mg, 13%):

MPt: 180-195°C;

MS m/e (AP$^+$): 468.12 (M$^+$ + H, 100%), 469.59 (M$^+$ + 2H, 20%);

MS m/e (AP$^-$): 467.56 (M$^-$, 45%), 466.60 (M$^-$ - H, 100%), 465.64 (M$^-$ - 2H, 88%);

IR (film): 3316, 2930,1651, 1602, 1515, 1430, 1106, 997, 816, 741 cm^{-1};

NMR (CDCl$_3$):δ = 1.25–1.70 (8H, m), 1.46 (3H, s), 2.00–2.10 (2H, m), 3.27 (1H, d, J=14.9 Hz), 3.30–3.48 (2H, m), 3.36 (1H, d, J=14.9 Hz), 4.43 (1H, s), 6.22 (2H, d, J=5.6 Hz), 6.85 (1H, d, J=2.0 Hz), 6.89–6.93 (1H, m), 7.11–7.37 (5H, m), 7.46–7.54 (2H, m), 8.08–8.13 (4H, m);

HPLC A: Rt. 7.21 min, 96.1/96.5% purity, 20-100% CH$_3$CN in H$_2$O (+0.1%TFA) over 15 min at 1mlmin^{-1}, Prodigy ODSIII 250x4.6mm 5µM, 215 and 254 nm;

HPLC B: Rt. 6.02 min, 99.1/100% purity, 80:20 methanol/Tris buffer at pH9, 1mlmin^{-1}, Prodigy ODSIII 250x4.6mm 5µM, 215 and 254 nm.

Example 19

(S)-3-(1*H*-Indol-3-yl)-2-(isoquinolin-4-ylamino)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide
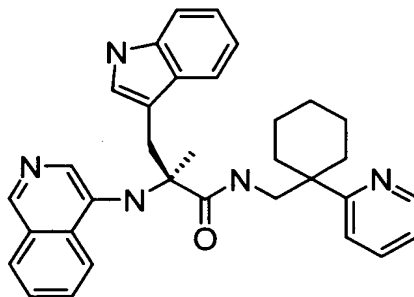
Example 19 was prepared on the same scale and using an analogous method as used for **Example 17**.

1.   The method of **Example 17** was followed except that 4-bromoisoquinoline (520mg, 2.5mmol) was used.

2.   The acid from step 1 (40mg, 0.12mmol), HBTU (46mg, 0.12mmol), and DIPEA (21µl, 0.12mmol) were stirred in DMF (10ml) for 5 minutes before adding DIPEA (21µl, 0.12mmol) and [1-(2- pyridyl)cyclohexyl]methylamine (WO 98/07718; 23mg, 0.12mmol). After 2 hours at ambient temperature the solvent was

removed under reduced pressure. The residue was taken up in ethyl acetate and washed with sodium bicarbonate solution (x2) and brine and dried (MgSO₄). The solvent was removed under reduced pressure. The crude product was purified by chromatography using 10g ISCO Redisep cartridge with 80% ethyl acetate in heptane as eluent. Repurification using 20g RP-C18 with 70% methanol in water and subsequent evaporation gave the desired product as a glass (9mg, 14%):

MPt: 98-101°C;

MS m/e (AP⁺): 518.28 (100%, M⁺ + H), 517.40 (M⁺, 50%);

MS m/e (AP⁻): 516.53 (75%, M⁻), 515.63 (100%, M⁻ - H);

IR (film): 3385, 3278, 3052, 2927, 2849, 1651, 1585, 1520, 1455, 1403, 1343, 781,740 cm⁻¹;

NMR (CDCl₃): δ= 1.20–1.65 (11H, m), 1.93–2.10 (2H, m), 3.35 (1H, d, J=14.6Hz), 3.39–3.52 (2H, m), 3.48 (1H, d, J=14.9 Hz), 4.62 (1H, s), 6.55–6.59 (1H, m), 6.90 (1H, d, J=2.0 Hz), 7.00 (1H, d, J=8.1 Hz), 7.17–7.28 (4H, m), 7.37–7.55 (4H, m), 7.62 (1H, s), 7.70 (1H, d, J=7.6 Hz), 7.74–7.76 (1H, m), 7.87 (1H, d, J=8.1 Hz), 8.15 (1H, s), 8.63 (1H, s)

HPLC A: Rt. 7.52 min, 100/100% purity, 20-100% CH₃CN in H₂O (+0.1%TFA) over 15 min at 1mlmin⁻¹, Prodigy ODSIII 250x4.6mm 5µM, 215 and 254 nm;

HPLC B: Rt. 8.33 min, 99.7/100% purity, 80:20 methanol/Tris buffer at pH9, 1mlmin⁻¹, Prodigy ODSIII 250x4.6mm 5µM, 215 and 254 nm;

Example 20

(S)-3-(1*H*-Indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-2-(pyrimidin-5-ylamino)-propionamide
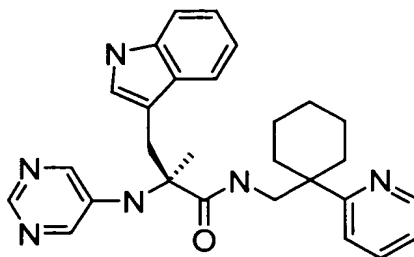
The above compound was prepared on the same scale and using an analogous method as used for **Example 17**.

1.   The method of **Example 17** was followed except that 5-bromopyrimidine (397mg, 2.5mmol) was used.

2.   The acid from step 1 (150mg, 0.5mmol), HBTU (190mg, 0.5mmol), and DIPEA (87µl, 0.5mmol) were stirred in DMF (10ml) for 5 minutes before adding DIPEA (87µl, 0.5mmol) and [1-(2-pyridyl)cyclohexyl]methylamine (WO 98/07718; 95mg, 0.5mmol). After 2 hours at ambient temperature the solvent was removed under reduced pressure. The residue was taken up in ethyl acetate and washed with sodium bicarbonate solution (x2) and brine and dried ($MgSO_4$). The solvent was removed under reduced pressure. The crude product was purified by chromatography using 10g ISCO Redisep cartridge with 90% ethyl acetate in heptane as eluent. Removal of the solvent under reduced pressure gave the desired product as a foam (135mg, 58%):

MPt: 95-98°C;

MS m/e (AP^+): 470.60 (25%), 469.58 (M^+ +H, 100%), 468.77 (M^+, 92%);

MS m/e (AP^-): 467.60 (M^- - H, 70%), 466.85 (100%);

IR (film): 3291, 3052, 2931, 2857, 1651, 1575, 1519, 1470, 1455, 1427, 1357, 1306, 1265, 1237, 1194, 1156, 1106, 1010, 848, 788, 739 cm^{-1};

NMR ($CDCl_3$): δ= 1.20–1.65 (8H, m), 1.48 (3H, s), 2.00–2.10 (2H, m), 3.24–3.48 (4H, m), 4.14 (1H, s), 6.88–6.92 (2H, m), 7.13–7.24 (3H, m), 7.37 (1H, d, J=8.1 Hz), 7.48–7.55 (3H, m), 7.86 (2H, s), 8.08–8.10 (1H, m), 8.16 (1H, s), 8.57 (1H, s);

HPLC A: Rt. 8.94 min, 99.3/99.4% purity, 20-100% CH_3CN in H_2O (+0.1%TFA) over 15 min at 1mlmin^{-1}, Prodigy ODSIII 250x4.6mm 5µM, 215 and 254 nm;

HPLC B: Rt. 5.76 min, 95.1/98.7% purity, 80:20 methanol/Tris buffer at pH9, 1mlmin^{-1}, Prodigy ODSIII 250x4.6mm 5µM, 215 and 254 nm.

Example 21

(S)-2-(Biphenyl-2-ylamino)-3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide
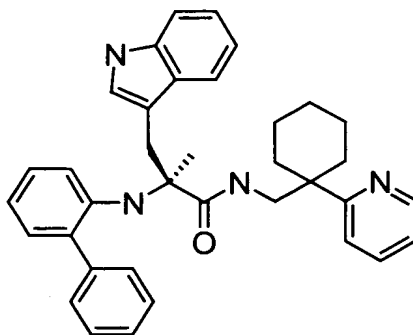
5   The above compound was prepared on the same scale and using an analogous method as used for **Example 17**.

1.   The method of **Example 18** except for the use of 2-bromo biphenyl (583mg, 2.5mmols).

10

2.   The acid from step 1 (350mg, 0.95mmol), HBTU (400mg, 1mmol), NEt$_3$ (0.5ml, 3.5mmol), and 1-(2- pyridyl)cyclohexyl]methylamine (WO   98/07718; 200mg, 1mmol) were stirred in DMF (15ml). After 1 hour at ambient temperature the reaction mixture was diluted with ethyl acetate (100ml), washed with sodium

15 bicarbonate solution (x2) and dried (MgSO$_4$). The solvent was removed under reduced pressure. The crude product was purified by chromatography using 0-50% ethyl acetate in heptane and then 0-30% dichloromethane in ether as eluent. Removal of the solvent under reduced pressure gave the desired product as a foam (98mg, 19% for step 2):

20   MS m/e (AP$^+$): 565 (M$^+$ + Na, 100%), 564 (80%), 542 (M$^+$, 30%)

IR (KBr disc): 3404, 2928, 2855, 1650, 1584, 1508, 1489, 1458, 1432 cm^{-1};

NMR (DMSO-d$_6$): δ = 1.10-1.52 (8H, m), 1.27 (3H, s), 1.95-2.05 (2H, m), 2.95 (1H, d, J=14.4 Hz), 3.02-3.08 (1H, m), 3.08 (1H, d, J=14.6 Hz), 3.28-3.34 (1H,

m), 4.36 (1H, s), 6.37 (1H, d, J=8 Hz), 6.49 (1H, d, J=2.2 Hz), 6.71-6.75 (1H, m), 6.82-6.86 (1H, m), 6.95-7.43 (13H, m), 7.52-7.57 (1H, m), 8.33 (1H, d, J=3.7 Hz), 10.81 (1H, s);

HPLC A: Rt. 12.65min, 99.65% purity, 20-100% CH_3CN in H_2O (+0.1%TFA) over 15 min at 1mlmin^{-1}, Prodigy ODSIII 250x4.6mm 5µM, 200-300 nm;

HPLC B: Rt. 33.05min, 99.89% purity, 80:20 methanol/Tris buffer at pH9, 1mlmin^{-1}, Prodigy ODSIII 250x4.6mm 5µM, 200-300 nm.

Example 22

(S)-3-(1H-Indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-2-m-tolylamino-propionamide
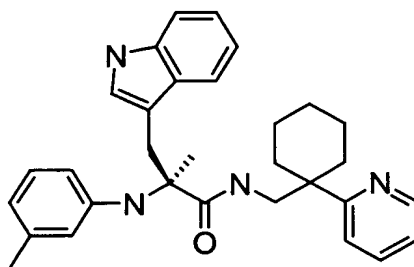
The above compound was prepared using a one-pot procedure analogous to the method used for **Example 16**. The synthesis was carried out on 1mmol scale using 1-bromo-3-methyl-benzene (171mg, 1mmol). The crude product was purified by chromatography using 25g NP silica with 25% ethyl acetate in heptane as eluent. Removal of the solvent under reduced pressure gave the desired compound as a glass (260mg, 54%):

MPt: 70-75°C;

MS m/e (AP$^+$): 481.33 (100%, M$^+$ + H), 482.37 (40%);

IR (film): 3385, 3291, 3049, 2929, 2857, 1652, 1607, 1590, 1513, 1456, 1431, 1341, 1302, 1264, 1237, 1177, 1155, 1104, 1010, 774, 741 cm^{-1};

NMR (DMSO-d$_6$): δ= 1.08–1.50 (8H, m), 1.19 (3H, s), 2.00–2.10 (2H, m), 2.16 (3H, s), 3.03 (1H, d.d, J=12.9 and 5.1 Hz), 3.10 (1H, d, J=14.7Hz), 3.22 (1H, d, J=14.6Hz), 3.24–3.30 (1H, m), 5.43 (1H, s), 6.29 (1H, s), 6.30 and 6.44 (each 1H,

each d, J=7.6 Hz), 6.87–7.07 (6H, m), 7.15–7.19 (1H, m), 7.29 (1H, d, J=8.0 Hz), 7.33 (1H, d, J=7.8 Hz), 7.48–7.54 (1H, m), 8.31–8.33 (1H, m), 10.81 (1H, s);

HPLC A: Rt. 11.04 min, 98.3% purity, 20-100% CH_3CN in H_2O (+0.1%TFA) over 15 min at 1mlmin^{-1}, Prodigy ODSIII 250x4.6mm 5μM, 200-300 nm;

HPLC B: Rt. 16.87 min, 99.5% purity, 80:20 methanol/Tris buffer at pH9, 1mlmin^{-1}, Prodigy ODSIII 250x4.6mm 5μM, 200-300 nm.

Example 23

(S)-3-(1*H*-Indol-3-yl)-2-methyl-2-(6-phenyl-pyridin-2-ylamino)-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide
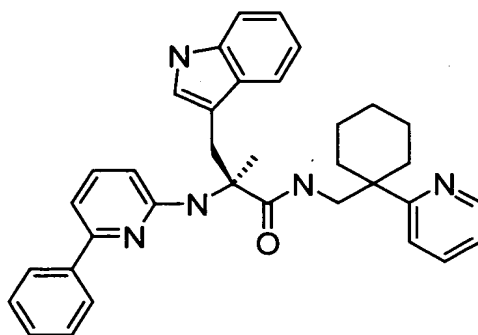
The above compound was prepared using a one-pot procedure analogous to the method used for **Example 16.** The synthesis was carried out on 0.4mmol scale using 2-bromo-6-phenyl-pyridine (95mg, 0.4 mmol). The crude product was purified by chromatography using 25g NP silica with 55% ethyl acetate in heptane as eluent. Removal of the solvent under reduced pressure gave the desired product as a foam (260mg, 54%):

MS m/e (AP$^+$) 544.31 (100%, M$^+$ + H), 545.35 (35%);

MS m/e (AP$^-$) 542.29 (100%, M$^-$ - H), 543.31 (M$^-$, 40%);

IR (film): 3407, 3276, 3056, 2930, 2857, 1651, 1595, 1576, 1519, 1486, 1467, 1455, 1439, 1339, 1264, 1180, 1157, 1105, 1028, 1009, 991, 804, 763, 739 cm^{-1};

NMR (CDCl$_3$) δ= 1.03–1.60 (8H, m), 1.53 (3H, s), 1.90-2.03 (2H, m), 3.32-3.45 (3H, m), 3.65 (1H, d, J=14.6Hz), 4.67 (1H, s), 6.13 (1H, d, J=8.3 Hz), 6.77–7.50 (14H, m), 7.97 (2H, d, J=7.1 Hz), 8.02 (1H, s), 8.23–8.25 (1H, m);

HPLC A: Rt. 4.21 min, 96.8% purity, 20-100% CH₃CN in H₂O (+0.1%TFA) over 7 min at 1.5mlmin⁻¹, Prodigy ODSIII 150x4.6mm 5μM, 200-300 nm.

Example 24

(R)-3-Phenyl-2-phenylamino-*N*-[1-pyridin-2-yl-cyclohexylmethyl)-propionamide
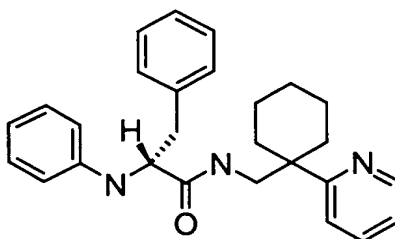
The above compound was synthesised as a two step process from **Intermediate 8** as shown in Scheme 4.

1. To a solution of **Intermediate 8** (0.5g, 3mmol) and bromobenzene (0.35ml, 3.3mmol) in DMA (5ml) under nitrogen was added potassium carbonate (0.6g, 4.3mmol) and copper (I) iodide (50mg, 0.26mmol) after which the mixture was heated to 90°C for 1.5 hours. Solvent was removed under reduced pressure and the residue was purified by flash chromatography eluting with 5% methanol in dichloromethane. Removal of solvent under reduced pressure gave (R)-3-phenyl-2-phenylamino-propionic acid as an oil (0.41g, 56%):

MS m/e (AP⁺): 242 (M⁺ + H, 100%).

2. The acid from step 1 (0.40g, 1.66mmol), HBTU (0.6g, 1.8mmol), and NEt₃ (0.5ml, 3.5mmol), and 1-(2-pyridyl)cyclohexyl]methylamine (WO 98/07718; 0.35mg, 1.8mmol) were stirred in DMF (15ml). After 1 hour at ambient temperature the reaction mixture was diluted with ethyl acetate (100ml), washed with sodium bicarbonate solution (x2) and dried (MgSO₄). The solvent was removed under reduced pressure. The crude product was purified by chromatography using 50% ethyl acetate in heptane and then RP C18 silica with 70% methanol in water as eluent.

Removal of the solvent under reduced pressure gave the desired product as a white amorphous solid (0.15g, 22%):

MPt: 113-115°C;

MS m/e (AP⁺): 414.22 (M⁺ + H, 100%);

IR (KBr disc): 3300, 2931, 2858, 1649, 1605, 1589, 1523, 1498, 1432, 1318, 748 cm⁻¹;

NMR (CDCl₃): δ = 1.20–1.70 (8H, m), 1. 90-2.15 (2H, m), 2.91 (1H, d.d, J=14.2 and 8.8 Hz), 3.27 (1H, d.d, J=14.2 and 4.4 Hz), 3.38 (1H, d.d, J=13.2 and 5.5 Hz), 3.48 (1H, d.d, J=13.2 and 6.1 Hz), 3.80 (1H, d, J=3.4 Hz), 3.88-3.93 (1H, m), 6.44 (2H, d, J=7.8 Hz), 6.74 (1H, t, J=11.3 Hz), 6.90-7.45 (11H,m), 8.28 (1H, d, J=3.6 Hz);

HPLC A: Rt. 4.51 min, 100% purity, 20-100% CH₃CN in H₂O (+0.1%TFA) over 10 min at 1.5 mlmin⁻¹, Prodigy ODSIII 250x4.6mm 5µM, 200-300 nm;

HPLC B: Rt. 13.15 min, 99.14% purity, 80:20 methanol/Tris buffer at pH9, 1mlmin⁻¹, Prodigy ODSIII 250x4.6mm 5µM, 200-300 nm.

Example 25

(S)-3-(1H-Indol-3-yl)-2-methyl-2-phenylethylamino-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide
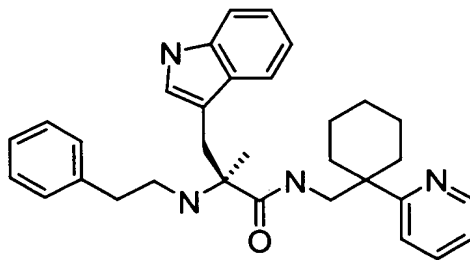
The above compound was prepared as shown in Scheme 5 via **Intermediate 10.**

1.   To a stirred solution of H-(S)-αMeTrp-OH (7) (10g, 46mmol) and di-t-butyl-dicarbonate (10g, 46mmol) in dioxan (100ml) was added water (20ml) and potassium

carbonate (10g, 74mmol). After 4 hours the reaction mixture was acidified with 2N hydrochloric acid (150ml) and product was extracted with ethyl acetate (2 x 200ml). The combined organic phases were dried (MgSO₄) and evaporated under reduced pressure. The residue was purified by flash chromatography using ethyl acetate as

5   eluent. Removal of solvent under reduced pressure gave Boc-(S)-αMeTrp-OH as an orange oil (14.5g, 99%). To a stirred solution of Boc-(S)-αMeTrp-OH (7g, 22mmol) in DMF (100ml) was added HBTU (8.0g, 22mmol), triethylamine (5ml, 35mmol), and [1-(2-pyridyl)cyclohexyl]methylamine (WO 98/07718; 4.2g, 22mmol). After 1 hour the reaction mixture was diluted with ethyl acetate (300ml), washed with 2N

10   hydrochloric acid (2 x 200ml), dried (MgSO₄) and evaporated under reduced pressure at 60°C. The residue was purified by flash chromatography. Elution with 5% methanol in dichloromethane and subsequent removal of solvent under reduced pressure gave intermediate **9** as yellow oil (8.3g, 77%):

MS m/e (AP+): 491 (M$^+$ + H, 100%), 513 (M$^+$ + Na, 20%);

15   IR (film): 3339, 2929, 2858, 1704, 1659, 1651, 1589, 1519, 1487, 1366, 1249, 1164, 1070, 908, 737 cm^{-1};

NMR (CDCl₃): δ = 1.20-1.70 (20H, m), 2.00-2.12 (2H, m), 3.25-3.50 (4H, m), 5.05-5.20 (1H, br.s), 6.92 (1H, d, J=2.0 Hz), 7.02-7.32 (6H, m), 7.51 (1H, d, J=8.0 Hz), 7.59-7.64 (1H, m), 8.03 (1H, s), 8.48 (1H, d, J=4 Hz).

20

2.   To a stirred solution of **Intermediate 9** (8.2g, 16.5mmol) in dichloromethane (100ml) was added trifluoroacetic acid (3.0ml, 39mmol). After 18 hours the solvent was removed under reduced pressure at 60°C. The residue was treated cautiously with saturated sodium carbonate solution (200ml) before extracting with ethyl acetate (3 x

25   200ml). The combined organic phases were dried (MgSO₄) and evaporated under reduced pressure at 60°C. The residue was purified by flash chromatography. Elution with 0-5% methanol in dichloromethane and subsequent removal of solvent under reduced pressure gave **Intermediate 10** as white foam (4.85g, 75%):

MPt: 65-68°C;

30   MS m/e (AP+): 391 (M$^+$ + H, 100%);

IR (KBr disc): 3367, 2926, 2855, 1648, 1589, 1569, 1522, 1455, 1430, 1366, 1341, 1234, 842, 784, 742 cm^{-1};

NMR (CDCl$_3$): δ = 1.20-1.80 (13H, m), 1.98-2.20 (2H, m), 2.83 (1H, d, J=14.2 Hz), 3.33 (1H, d, J=14.2 Hz), 3.38 (2H, d, J=5.6 Hz), 6.98-7.20 (6H, m), 7.50-7.75 (3H, m), 8.05-8.15 (1H, s), 8.49-8.51 (1H, m);

5   3.   To a stirred solution of **Intermediate 10** (293mg, 0.75mmol) and phenacetaldehyde (90mg, 0.75mmol) in 1,2-dichloroethane (20ml) was added solid sodium triacetoxyborohydride (316mg, 1.5mmol). After stirring overnight, saturated sodium bicarbonate solution was added – effervescence was observed. The aqueous phase was extracted with dichloromethane. The combined organic phases were dried 10   (MgSO$_4$) and solvent was removed under reduced pressure. The residue was purified by chromatography using 20g RP-C18 with 0-50% methanol in water followed by 20g NP silica with 45% ethyl acetate in heptane. Removal of solvent under reduced pressure gave the desired compound as a glass (60mg, 16%):

MS m/e (ES$^+$): 496.56 (28%), 495.5 (52%, M$^+$ + H), 364.43 (22%), 269.34 15   (51%), 268.90 (88%), 248.37 (100%);

IR (film): 3274, 3058, 2928, 2856, 1651, 1588, 1568, 1519, 1469, 1454, 1431, 1355, 1263, 1236, 1155, 1117, 1053, 1030, 1009, 992, 930, 782, 742 cm^{-1};

^{1}H NMR (CDCl$_3$): δ = 1.20-1.65 (11H, m), 2.00-2.20 (2H, m), 2.40-2.75 (4H, m), 2.94 and 3.05 (each 1H, each d, J=14.4 Hz), 3.41 (2H, d, J=6.1 Hz), 6.74 (1H, d, J=2.2 Hz), 7.04-7.25 (9H, m), 7.32 (1H, d, J=7.8 Hz), 7.55-7.60 (3H, m), 7.90 (1H, s), 20   8.55-8.58 (1H, m);

HPLC A: Rt. 8.52 min, 99.0/98.6% purity, 20-100% CH$_3$CN in H$_2$O (+0.1%TFA) over 15 min at 1mlmin^{-1}, Prodigy ODSIII 250x4.6mm 5μM, 215 and 254 nm;

25   HPLC B: Rt. 23.84 min, 99.6/100% purity, 80:20 methanol/Tris buffer at pH9, 1mlmin^{-1}, Prodigy ODSIII 250x4.6mm 5μM, 215 and 254 nm.

Example 26

(S)-2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide

5
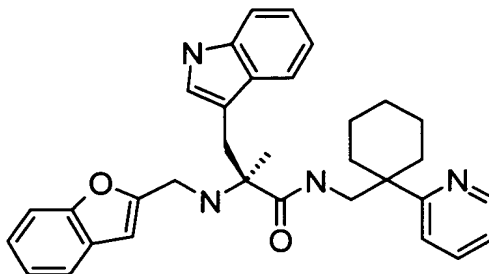
The above compound was prepared as shown in Scheme 5 via **Intermediate 10**.

To a stirred solution of **Intermediate 10** (150mg, 0.38mmol) and benzofuran-2-
10   carbaldehyde (56mg, 0.38mmol) in 1,2-dichloroethane (5ml) was added solid sodium
triacetoxyborohydride (162mg, 0.77mmol). After stirring at room temperature for 48
hours saturated sodium bicarbonate solution was added – effervescence was observed.
The aqueous phase was extracted with ethyl acetate. The combined organic phases
were dried (MgSO$_4$) and solvent removed under reduced pressure. The residue was
15   purified by chromatography using 60% ethyl acetate in heptane. Removal of solvent
under reduced pressure gave the desired product as an amorphous white solid (29mg,
15%):

MS m/e (ES$^+$): 521.08 (M$^+$ + H, 100%), 391.06 (50%);

IR (film): 3268, 3056, 2930, 2856, 1656, 1588, 1569, 1519, 1469, 1454, 1431,
20   1355, 1342, 1255, 1171, 1105, 1052, 1009, 909, 788, 740 cm^{-1};

^{1}H NMR (CDCl$_3$): δ = 1.20-2.20 (14H, m), 3.08 (1H, d, J=14.4 Hz), 3.14 (1H,
d, J=14.8 Hz), 3.45-3.49 (2H, m), 3.66 (1H, d, J=14.4 Hz), 3.76 (1H, d, J=14.8 Hz),
6.33 (1H, s), 6.84-6.88 (1H, m), 7.00-7.65 (12H, m), 8.32 (1H, s), 8.39 (1H, d, J=4.0
Hz);

HPLC A: Rt. 8.86 min, 99.7/99.1% purity, 20-100% CH$_3$CN in H$_2$O (+0.1%TFA) over 15 min at 1mlmin^{-1}, Prodigy ODSIII 250x4.6mm 5μM, 215 and 254 nm.

<p style="text-align:center">Example 27</p>

(S)-3-(1H-Indol-3-yl)-2-methyl-2-(4-nitro-benzylamino)-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide
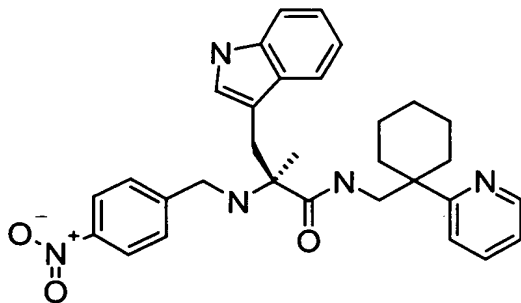
The above compound was prepared as shown in Scheme 5 via **Intermediate 10**. To a stirred solution of **Intermediate 10** (150mg, 0.38mmol) and 4-nitrobenzaldehyde (58mg, 0.38mmol) in 1,2-dichloroethane (5ml) was added solid sodium triacetoxyborohydride (114mg, 0.54mmol). After stirring at room temperature for 24 hours saturated sodium bicarbonate solution was added – effervescence was observed. The aqueous phase was extracted with ethyl acetate. The combined organic phases were dried (MgSO$_4$) and solvent removed under reduced pressure. The residue was purified by chromatography using 60% ethyl acetate in heptane. Repurifcation using RP silica with 45% methanol in water (+ 1% acetic acid) gave pure product. The pure fractions were combined, basified (sodium carbonate), and extracted with ethyl acetate. Removal of solvent under reduced pressure gave the desired compound as a glass (10.5mg, 5%):

MPt: 58-60°C;

MS m/e (ES$^+$): 526.15 (M$^+$ + H, 100%), 527.14 (33%);

IR (film): 3365, 2924, 2856, 1652, 1513, 1429, 1346, 1257, 1048 cm^{-1};

^{1}H NMR (DMSO-d_6): δ = 1.10-1.55 (8H, m), 1.19 (3H, s), 1.88-2.08 (2H, m), 2.25-2.30 (1H, m), 2.95-3.02 (2H, m), 3.10-3.20 (1H, m), 3.17-3.27 (1H, m), 3.50-3.80

(2H, m), 6.93-7.63 (11H, m), 8.12 (2H, d, J=8.8 Hz), 8.42 (1H, d, J=3.6 Hz), 10.86 (1H, s).

Example 28

BB$_1$ and BB$_2$ Binding Assays

In the following experiments, measurement of BB$_1$ and BB$_2$ binding was as follows. CHO-K1 cells stably expressing cloned human NMB (for (BB$_1$ assay) and GRP receptors (for BB$_2$ assay) were routinely grown in Ham's F12 culture medium supplemented with 10% foetal calf serum and 2 mM glutamine. For binding experiments, cells were harvested by trypsinization, and stored frozen at -70°C in Ham's F12 culture medium containing 5% DMSO until required. On the day of use, cells were thawed rapidly, diluted with an excess of culture medium, and centrifuged for 5 minutes at 2000 g. Cells were resuspended in 50 mM Tris-HCl assay buffer (pH 7.4 at 21°C, containing 0.02% BSA, 40μg/mL bacitracin, 2μg/mL chymostatin, 4μg/mL leupeptin, and 2μM phosphoramidon), counted, and polytronned (setting 5, 10 sec) before centrifuging for 10 minutes at 28,000 g. The final pellet was resuspended in assay buffer to a final cell concentration of 1.5×10^5/mL. For binding assays, 200μL aliquots of membranes were incubated with [^{125}I][Tyr^4]bombesin (<0.1 nM) in the presence and absence of test compounds (final assay volume 250μL) for 60 minutes and 90 minutes for NMB and GRP receptors, respectively. Nonspecific binding was defined by 1μM bombesin. Assays were terminated by rapid filtration under vacuum onto Whatman GF/C filters presoaked in 0.2% PEI for >2 hours, and washed 50 mM Tris-HCl (pH 6.9 at 21°C; 6 × 1 mL). Radioactivity bound was determined using a gamma counter.

All competition data was analysed using nonlinear regression utilizing iterative curve-plotting procedures in Prism® (GraphPad Software Inc., San Diego, USA). IC$_{50}$ values were corrected to K$_i$ values using the Cheng-Prusoff equation (Cheng Y., Prusoff W. H., *Biochem. Pharmacol.* 22: 3099-3108, 1973).

The results obtained are listed in Table 1.

Table 1 : Human NMB and GRP receptor binding affinities

Example No.	NMB K_i (nM)	GRP K_i (nM)
9	4	24
10	469	
11	5580	
12	16	2820
13	19	1385
14	106	1190
15	213	1770
16	15	
17	2080	
18	303	
19	1249	
20	3163	
21	824	
22	653	
23	3371	
24	137	
25	616	2620
26	2400	
27	652	

5

Example 29

Effect of (S)-3-(1*H*-Indol-3-yl)-*N*-[1-(5-methoxy-pyridin-2-yl)-cyclohexylmethyl]-2-methyl-2-[4-(4-nitro-phenyl)-oxazol-2-ylamino]-propionamide (Compound (2))

10   **in PEG200 on female rat sexual proceptivity**

Ovariectomised adult female Sprague Dawley rats (180-200g, from Charles River) were housed in groups of 6 in a reversed lighting system of 12h light:dark (lights off 7.00-19.00h). Two weeks after ovariectomy they were used for sexual activity tests. Animals were adapted to the apparatus (in the absence of stimuli

5   animals) for 10min on 2 consecutive days prior to testing. The experiments started at least 5h into the dark period.

Tests were carried out in a circular arena of 90cm diameter, surrounded by a 30cm high wall. Two small cages with wire-mesh front (15x15cm) are fixed into the

10   wall such that the front of the cage is "flush" with the wall and the 2 cages are opposite each other. They contain two stimuli animals: an intact sexually experienced male and a receptive female (ovariectomised, primed with 5μg oestradiol benzoate dissolved in corn oil and injected subcutaneously 48 hours before the test and with 0.5 mg of progesterone four hours before the test). Sexually naive test and control animals

15   were used. Forty eight hours before the tests, both the test and control animals were primed with 5μg oestradiol benzoate. Test animals were treated with the above compound (30-100mg/kg) which was dissolved in PEG 200 vehicle and administered orally in a 1ml/kg volume 1h before each test. For animals used as positive controls, progesterone (0.5mg/0.1ml) was dissolved in corn oil and administered

20   subcutaneously (s.c.), 4h before the test. Test and control animals were introduced one at a time for 10 minute periods into the arena. During the 10min test, the time that the test or positive control animal spent investigating each stimulus animal was noted. The arena was thoroughly cleaned between animals. The position of the male/female stimuli boxes was randomised between animals, in order to avoid place preference.

25   The difference in the percentage of time spent investigating male minus female was calculated, out of the total time spent investigating stimuli animals.

It was found (see **Figure 19**) that the above compound dose-dependently (30-100) increased the percentage of time spent investigating the male stimulus, with a

30   MED of 100mg/kg (see below). The effect of this dose was similar to the effect of progesterone (maximal). (*P<0.05, **P<0.01 Kruskal-Wallis followed by Mann-Whitney test, vs vehicle).

Example 30

Effect of Compound (2) in methyl cellulose on female rat sexual proceptivity.

5   Example 31 was repeated except that the above compound (3-30 mg/kg) was dissolved in 0.5% methyl cellulose and was administered p.o. in a dosing volume of 3ml/kg 1h before tests. Progesterone, (0.5mg/0.1ml) was dissolved in corn oil and administered s.c., 4h before test, as a positive control.

10   The above compound dose-dependently (3-30mg/kg) increased the percentage of time spent investigating the male stimulus, with a MED of 10mg/kg. This represents a 10-fold increase in potency compared to the oral results obtained in the PEG200 vehicle (MED=100mg/kg). The results are shown in **Figure 20** in which bars represent percentage of time spent investigating male, minus the percentage of time 15   spent investigating the female stimuli±SEM, (n=6-9 per group). *$P<0.05$, **$P<0.01$ *vs* vehicle (One-way ANOVA followed by Dunnett's test *vs* vehicle group).

Example 31

Effect of Compound (2) in PEG 200 on female rat sexual receptivity.

20

      Ovariectomised adult female Sprague Dawley rats (180-200g, from Charles River) were housed in groups of 6 in a reversed lighting system of 12h light:dark (lights off 7.00-19.00h). Two weeks after ovariectomy they were used for sexual activity tests. The experiments started at least 5h into the dark period.

25

      The above compound was dissolved in PEG200 vehicle and administered orally. Quinelorane dihydrochloride (LY 163,502, 6.25μg/kg) was dissolved in water and administered subcutaneously (s.c.), as a positive control. Both compounds were administered in a 1ml/kg volume.

30

Forty eight hours before tests, the animals were primed with 5μg oestradiol benzoate (Sigma Chemical. Co. Ltd., UK) dissolved in corn oil and injected subcutaneously. The females were placed with a series of vigorous male rats and subjected to 10 mounts. The lordotic response of the animal was recorded and expressed as a percentage of the mounts (i.e. lordosis quotient, LQ). Treatment induced LQ=0-10% in most of the animals, which were considered non-receptive (NR). Animals showing higher LQ were not included in the study. Each rat was tested prior to administration of the compound and then tested similarly at 1h and 90min post-injection of the above compound or quinelorane respectively.

A single administration of quinelorane (6.25μg/kg) significantly (P<0.01) increased the LQ, 90min after administration, compared to the LQ shown before administration (paired t test). A single oral administration of the above compound dose-dependently (10-100mg/kg) increased the LQ 1h after administration, with a MED of 100mg/kg (P<0.01) compared to the LQ shown before administration (paired t test). The effect of the above compound (100mg/kg) was similar to the effect of quinelorane (6.25μg/kg) as is shown in **Figure 21**.

Synthesis Example (compounds of formula (III))

(S)-2-Amino-3-(1 *H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide (Intermediate III-7) and
(S)-2-Amino-3-(1 *H*-indol-3-yl)-2-methyl-*N*-(1-(5-methoxy-pyridin-2-yl)-cyclohexylmethyl)-propionamide (Intermediate III-6)

In reaction scheme 7 below, Intermediates III-6 and III-7 are made by (i) protecting the amino group of the starting amino acid **a** with di-*t*-butyl carbonate and potassium carbonate in dioxane/water, (ii) forming an amide by reaction of the *N*-protected amino acid with an amine **b1** or **b2** in dimethylformamide in the presence of *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HBTU) and *N,N*-diisopropyl-ethylamine (DIPEA), and (iii) deprotecting the amino group of the product **c1** or **c2** by reaction with trifluoroacetic acid in dichloromethane.

Scheme 7

a

b1 R = H
b2 R = OMe

c1 R = H
c2 R = OMe

Intermediate III-7 R = H
Intermediate III-6 R = OMe
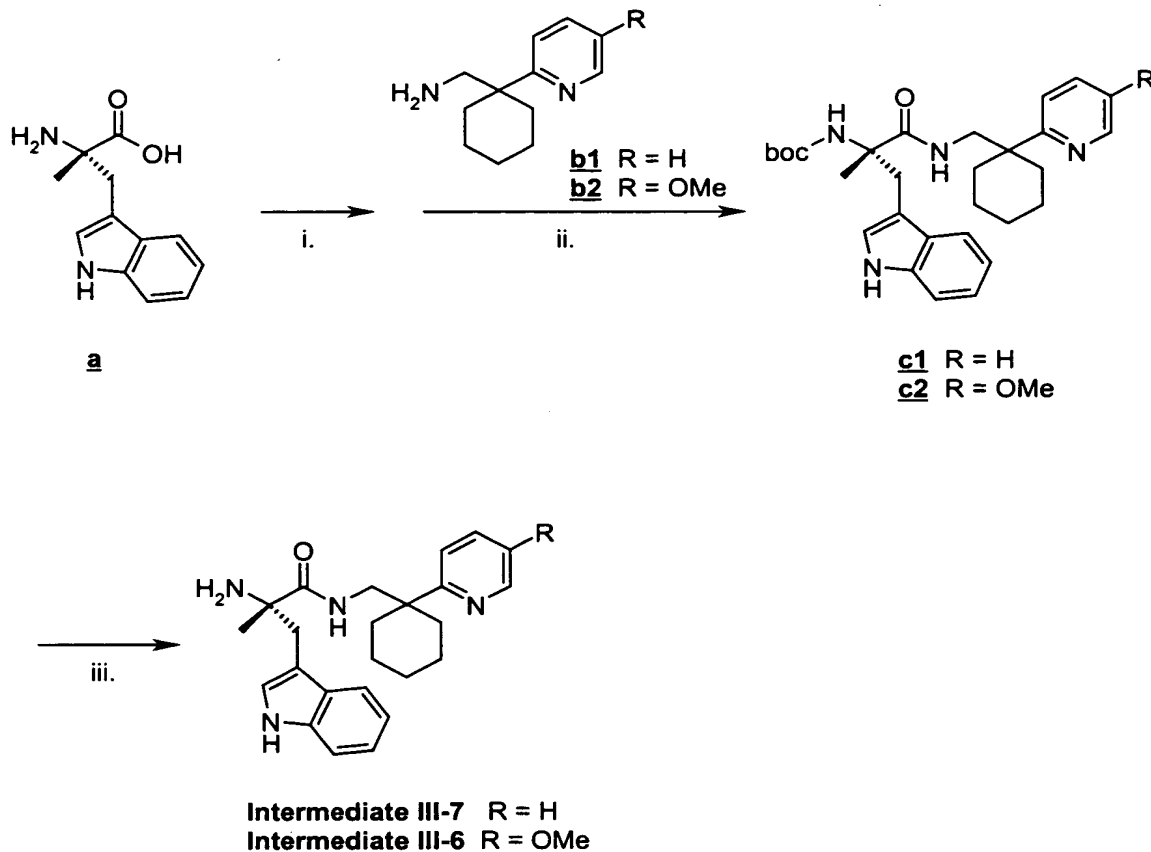
5 i.   BOC$_2$O, K$_2$CO$_3$, dioxane, water

   ii.   HBTU, DIPEA, DMF

   iii.   TFA, CH$_2$Cl$_2$

10 {(S)-2-(1-*H*-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid *tert*-butyl ester (**c1**)

(1)   To a stirred solution of H-(S)-αMeTrp-OH (**a**) (10g, 46mmol) and di-t-butyl-dicarbonate (10g, 46mmol) in dioxane (100ml) was added water (20ml) and

15 potassium carbonate (10g, 74mmol). After 4 hours the reaction mixture was acidified with 2N hydrochloric acid (150ml) and product extracted with ethyl acetate (2 x 200ml). The combined organic phases were dried (MgSO$_4$) and evaporated under

reduced pressure. The residue was purified by flash chromatography, eluting with ethyl acetate. Removal of solvent under reduced pressure gave Boc-(S)-αMeTrp-OH as orange oil (14.5g, 99%).

5   (2)   To a stirred solution of Boc-(S)-αMeTrp-OH (7g, 22mmol) in DMF (100ml) was added HBTU (8.0g, 22mmol), triethylamine (5ml, 35mmol), and [1-(2-pyridyl)cyclohexyl]methylamine (**b1**, 4.2g, 22mmol, described in WO 98/07718). After 1 hour the reaction mixture was diluted with ethyl acetate (300ml) and washed with 2N hydrochloric acid (2 x 200ml), dried (MgSO$_4$) and evaporated under reduced 10   pressure at 60°C. The residue was purified by flash chromatography. Elution with 5% methanol in dichloromethane and subsequent removal of solvent under reduced pressure gave **c1** as yellow oil (8.3g, 77%):

IR (film): 3339, 2929, 2858, 1704, 1659, 1651, 1589, 1519, 1487, 1366, 1249, 1164, 1070, 908, 737 cm^{-1};

15   NMR (CDCl$_3$): δ = 1.20-1.70 (20H, m), 2.00-2.12 (2H, m), 3.25-3.50 (4H, m), 5.05-5.20 (1H, br.s), 6.92 (1H, d, J=2.0 Hz), 7.02-7.32 (6H, m), 7.51 (1H, d, J=8.0 Hz), 7.59-7.64 (1H, m), 8.03 (1H, s), 8.48 (1H, d, J=4 Hz);

MS m/e (AP+): 491 (M$^+$ + H, 100%), 513 (M$^+$ + Na, 20%).

20   (3)   **(S)-2-Amino-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexyl methyl)-propionamide (Intermediate III-7)**

To a stirred solution of **c1** (8.2g, 16.5mmol) in dichloromethane (100ml) was added trifluoroacetic acid (3.0ml, 39mmol). After 18 hours the solvent was removed 25   under reduced pressure at 60°C. The residue was treated cautiously with saturated sodium carbonate solution (200ml) before extracting with ethyl acetate (3 x 200ml). The combined organic phases were dried (MgSO$_4$) and evaporated under reduced pressure at 60°C. The residue was purified by flash chromatography. Elution with 0-5% methanol in dichloromethane and subsequent removal of solvent under reduced 30   pressure gave **Intermediate III-7** as white foam (4.85g, 75%).

MPt: 65-68°C;

IR (KBr disc): 3367, 2926, 2855, 1648, 1589, 1569, 1522, 1455, 1430, 1366, 1341, 1234, 842, 784, 742 cm^{-1};

NMR (CDCl$_3$): δ = 1.20-1.80 (13H, m), 1.98-2.20 (2H, m), 2.83 (1H, d, J=14.2 Hz), 3.33 (1H, d, J=14.2 Hz), 3.38 (2H, d, J=5.6 Hz), 6.98-7.20 (6H, m), 7.50-

5   7.75 (3H, m), 8.05-8.15 (1H, s), 8.49-8.51 (1H, m);

MS m/e (AP+): 391 (M$^+$ + H, 100%).

{(S)-2-(1-_H_-Indol-3-yl)-1-methyl-1-[(1-(5-methoxy-pyridin-2-yl)-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid _tert_-butyl ester (_c2_)

10

To a stirred solution of Boc-(S)-αMeTrp-OH (1.44g, 4.5mmol) in DMF (50ml) was added HBTU (1.72g, 4.5mmol), DIPEA (2.38ml, 13.6mmol), and [1-(5-methoxy-2-pyridyl)cyclohexyl]methanamine (1g, 4.5mmol). After over night the reaction mixture was diluted with ethyl acetate (300ml) and water, dried (MgSO$_4$) and

15   evaporated under reduced pressure. The residue was purified by flash chromatography. Elution with ethylacetate/heptane (1:1) and subsequent removal of solvent under reduced pressure gave _c2_ as an oil (2.207g, 94%).

NMR (CDCl$_3$): δ = 1.24-1.60 (8H, m), 1.39 (9H, s), 1.52 (3H, s), 2.00-2.18 (2H, m), 3.20-3.43 (4H, m), 3.82 (3H, s), 6.92 (1H, d, J=2.4 Hz), 7.02-7.20 (6H, m),

20   7.30 (1H, d, J=6.0 Hz), 7.51 (1H, d, J=8Hz), 8.00 (1H, s), 8.17 (1H, d, J=2.8Hz).

MS m/e (ES+): 521.36 (M$^+$ + H, 100%), 543.25 (M$^+$ + Na).

Intermediate III-6

25   To a stirred solution of _c2_ (2.2g, 4.2mmol) in dichloromethane (10ml) was added trifluoroacetic acid (5ml, excess). After stirring over night the reaction mixture was taken up in 1N HCl and extracted with diethylether. Organic phase discarded. The aqueous phase was basified cautiously with saturated sodium carbonate solution before extracting with ethyl acetate (3 x 50ml). The combined organic phases were

30   dried (MgSO$_4$) and evaporated under reduced pressure at 60°C to give **Intermediate III-6** as a glass (1.253g, 71%).

IR (film): 3272, 2930, 2857, 1651, 1595, 1573, 1520, 1489, 1478, 1455, 1393, 1358, 1291, 1268, 1232, 1181, 1150, 1131, 1030, 1012, 831, 741 cm^{-1};

NMR (DMSO): δ = 1.10-1.65 (13H, m), 1.80-1.90 (1H, m), 2.00-2.10 (1H, m), 2.70 (1H, d, J=13.9 Hz), 3.10 (1H, d, J=13.9 Hz), 3.10-3.22 (2H, m), 3.77 (3H,s), 6.93-7.07 (4H, m), 7.16-7.19 (1H, m), 7.32 (1H, d, J=8.1 Hz), 7.48-7.55 (2H, m), 8.21 (1H, d, J=3.2 Hz), 10.88 (1H, s);

MS m/e (ES+): 421.27 (M$^+$ + H, 100%), 443.26 (M$^+$ + Na).

Examples 32-86

N-acyl derivatives of Intermediate III-6 and III-7

Scheme 8 describes the synthesis of N-acyl derivatives of **Intermediates III-7** and **III-6**.

Scheme 8

Examples 32-85

Example 86
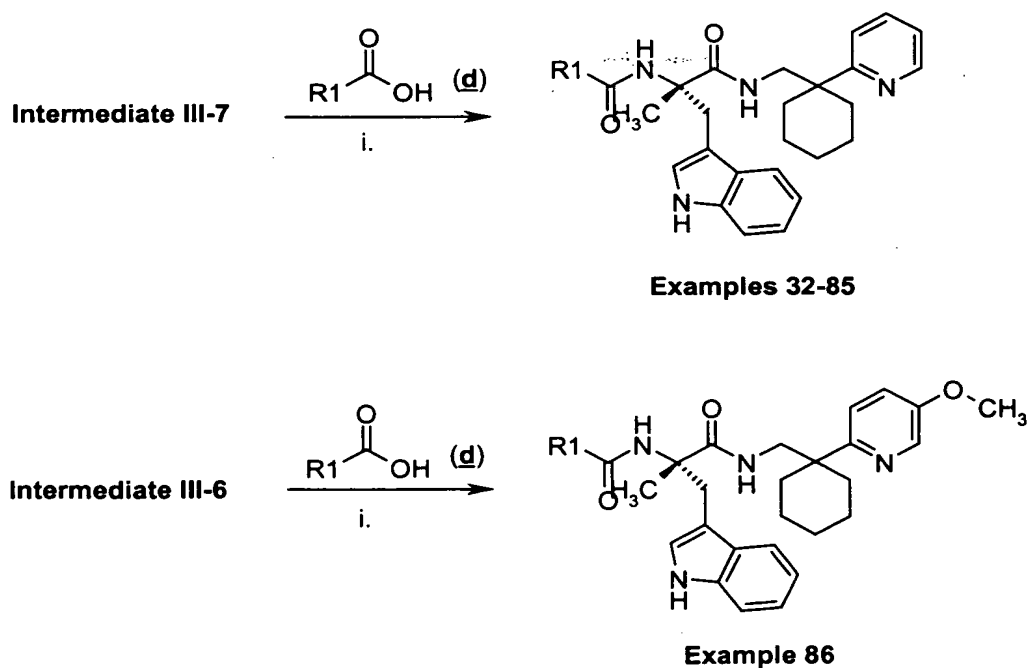
i.   HBTU, DIPEA, DMF

In scheme 8, R1 represents the rest of the carboxylic acid d molecule. These intermediates d are listed in table 2.

N-acyl derivatives of Intermediate III-7

To acid **d** (0.18 mmol) was added 0.50 M HBTU in DMF (300 µL, 0.15

5 mmol), 1.0 M diisopropylethylamine in DMF (300 µL, 0.30 mmol) and 0.40 M

Intermediate III-7 in DMF (375 µL, 0.15 mmol). The solution was shaken on an

orbital shaker at room temperature for 18 h. Water (1.0 mL) was added and the

mixture was loaded onto a LC-18 SPE cartridge (0.5 g sorbent) and the cartridge was

eluted with water (3 mL), 25% methanol/water (3 mL), 50% methanol/water (4 mL)

10 and methanol (4.5 mL)). The methanol fraction was concentrated and analysed by

LCMS. When the purity was <90% the product was further purified by prep. HPLC

(column: Phenomenex primesphere 10 µ C18-HC 110A, 100x21.20 mm; mobile

phase: methanol / water 10 to 100% gradient). The products were characterised and

analysed by LCMS (column: 50x4.6 mm Prodigy ODSIII (5µ) column; mobile phase:

15 acetonitrile / water (0.1% formic acid) 5 to 100% gradient over 2 min, held at 100%

acetonitrile for 1 min; flow rate 4 mL/min; UV detection at 215 nm; mass spec: 150-

900 Da full scan APCI+ centroid data)

The following products were made by the above method, with the starting

20 material listed in Table 2 and gave the test results indicated in Table 3:

TABLE 2

Example	Intermediate d
32	Benzoic acid
33	4-Methyl-benzoic acid
34	4-Chloro-benzoic acid
35	4-Methoxy-benzoic acid
36	4-Nitro-benzoic acid
37	4-Methanesulfonyl-benzoic acid

38	3-Cyano-benzoic acid
39	3-Chloro-benzoic acid
40	3-Methoxy-benzoic acid
41	3-Methanesulfonyl-benzoic acid
42	3-Dimethylamino-benzoic acid
43	3-Methyl-benzoic acid
44	2-Chloro-benzoic acid
45	2-Nitro-benzoic acid
46	2-Methoxy-benzoic acid
47	2-Methyl-benzoic acid
48	2-Dimethylamino-benzoic acid
49	2-Fluoro-benzoic acid
50	*p*-Tolyl-acetic acid
51	*o*-Tolyl-acetic acid
52	(4-Hydroxy-phenyl)-acetic acid
53	(3-Hydroxy-phenyl)-acetic acid
54	*m*-Tolyl-acetic acid
55	(2-Fluoro-phenyl)-acetic acid
56	Thiophen-3-yl-acetic acid
57	Pyridine-2-carboxylic acid
58	Isonicotinic acid
59	Furan-3-carboxylic acid
60	Furan-2-carboxylic acid
61	1*H*-Indole-2-carboxylic acid
62	5-Methyl-isoxazole-3-carboxylic acid
63	1-Methyl-1*H*-pyrrole-2-carboxylic acid
64	Thiophene-2-carboxylic acid

65	Thiophene-3-carboxylic acid
66	1*H*-Indole-6-carboxylic acid
67	1*H*-Indole-5-carboxylic acid
68	1*H*-Indole-4-carboxylic acid
69	1*H*-Indole-7-carboxylic acid
70	1-Methyl-1*H*-indole-2-carboxylic acid
71	Benzo[*b*]thiophene-2-carboxylic acid
72	Benzothiazole-6-carboxylic acid
73	1*H*-Benzotriazole-5-carboxylic acid
74	3-Methyl-thiophene-2-carboxylic acid
75	5-Methyl-thiophene-2-carboxylic acid
76	6-Methyl-pyridine-2-carboxylic acid
77	Isoquinoline-3-carboxylic acid
78	Quinoxaline-2-carboxylic acid
79	Quinoline-8-carboxylic acid
80	5-Phenyl-oxazole-4-carboxylic acid
81	2-Pyrrol-1-yl-benzoic acid
82	(4-Methoxy-phenyl)-acetic acid
83	(4-Dimethylamino-phenyl)-acetic acid
84	(2-Nitro-phenyl)-acetic acid
85	(2-Methoxy-phenyl)-acetic acid
86	1*H*-Indole-2-carboxylic acid

TABLE 3

Example No	Product	MH⁺	Purity %	LCMS Ret time (min)	BB1 IC50 (nM)	BB2 IC50 (nM)
32	N-{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-benzamide	494,64	100	1.71	2499	IA
33	N-{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-4-methyl-benzamide	508,67	95	1.76	2499	IA
34	4-Chloro-N-{(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexyl-methyl)-carbamoyl]-ethyl}-benzamide	529,09	94	1.84	1349	IA
35	N-{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-4-methoxy-benzamide	524,67	94	1.68	2879	IA
36	N-{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-4-nitro-benzamide	539,64	80	1.79	343	IA
37	N-{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-4-methanesulfonyl-benzamide	572,73	95	1.60	2272	IA
38	3-Cyano-N-{(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-benzamide	519,65	91	1.71	2042	IA
39	3-Chloro-N-{(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexyl-methyl)-carbamoyl]-ethyl}-benzamide	529,09	97	1.84	1269	IA
40	N-{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-3-methoxy-benzamide	524,67	98	1.73	2859	IA

41	N-{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-3-methanesulfonyl-benzamide	572,73	95	1.60	3051	IA
42	Dimethylamino-N-{(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexyl-methyl)-carbamoyl]-ethyl}-benzamide	537,71	91	1.74	2518	IA
43	N-{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-3-methyl-benzamide	508,67	100	1.79	2351	IA
44	2-Chloro-N-{(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexyl-methyl)-carbamoyl]-ethyl}-benzamide	529,09	98	1.79	3229	IA
45	N-{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-2-nitro-benzamide	539,64	91	1.71	4581	IA
46	N-{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-2-methoxy-benzamide	524,67	100	1.73	2559	IA
47	N-{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-2-methyl-benzamide	508,67	100	1.79	3283	IA
48	C-Dimethylamino-N-{(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexyl-methyl)-carbamoyl]-ethyl}-benzamide	537,71	93	1.79	716	IA
49	2-Fluoro-N-{(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-benzamide	512,63	98	1.76	3949	IA
50	(S)-3-(1H-Indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-2-(2-p-tolyl-ethanoylamino)-propionamide	522,70	94	1.76	944	IA
51	(S)-3-(1H-Indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-2-(2-o-tolyl-ethanoylamino)-propionamide	522,70	98	1.76	944	IA

52	(S)-2-[2-(4-Hydroxy-phenyl)-ethanoylamino]-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	524,67	96	1.50	3135	IA
53	(S)-2-[2-(3-Hydroxy-phenyl)-ethanoylamino]-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	524,67	90	1.52	1437	IA
54	(S)-3-(1H-Indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-2-(2-m-tolyl-ethanoylamino)-propionamide	522,70	95	1.76	817	IA
55	(S)-2-[2-(2-Fluoro-phenyl)-ethanoylamino]-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	526,66	94	1.71	878	1546
56	(S)-3-(1H-Indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-2-(2-thiophen-3-yl-ethanoylamino)-propionamide	514,70	93	1.65	1437	IA
57	Pyridine-2-carboxylic acid {(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide	495,63	98	1.68	3709	IA
58	N-{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-isonicotinamide	495,63	98	1.47	1365	IA
59	Furan-3-carboxylic acid {(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide	484,60	97	1.60	1204	IA
60	Furan-2-carboxylic acid {(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide	484,60	100	1.60	1204	IA
61	1H-Indole-2-carboxylic acid {(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide	533,68	100	1.79	289	527
62	5-Methyl-isoxazole-3-carboxylic acid {(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide	499,62	94	1.46	4127	IA

63	1-Methyl-1H-pyrrole-2-carboxylic acid {(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide	497,65	96	1.46	4819	-
64	Thiophene-2-carboxylic acid {(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide	500,67	100	1.42	1437	IA
65	Thiophene-3-carboxylic acid {(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide	500,67	100	1.39	2201	IA
66	1H-Indole-6-carboxylic acid {(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide	533,68	100	1.42	1604	IA
67	1H-Indole-5-carboxylic acid {(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide	533,68	100	1.35	1881	IA
68	1H-Indole-4-carboxylic acid {(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide	533,68	99	1.35	4503	IA
69	1H-Indole-7-carboxylic acid {(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide	533,68	100	1.60	1369	IA
70	1-Methyl-1H-indole-2-carboxylic acid {(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide	547,71	100	1.70	1233	IA
71	Benzo[b]thiophene-2-carboxylic acid {(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide	550,73	100	1.63	611	IA
72	Benzothiazole-6-carboxylic acid {(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide	551,72	95	1.35	897	1495
73	1H-Benzotriazole-5-carboxylic acid {(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide	535,65	95	1.25	3167	-

74	3-Methyl-thiophene-2-carboxylic acid {(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide	514,70	100	1.53	744	IA
75	5-Methyl-thiophene-2-carboxylic acid {(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide	514,70	100	1.60	1663	IA
76	6-Methyl-pyridine-2-carboxylic acid {(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide	509,66	98	1.6	2816	IA
77	Isoquinoline-3-carboxylic acid {(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide	545,69	100	1.71	1363	-
78	Quinoxaline-2-carboxylic acid {(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide	546,68	94	1.67	1425	IA
79	Quinoline-8-carboxylic acid {(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide	545,69	96	1.57	4479	IA
80	5-Phenyl-oxazole-4-carboxylic acid {(S)-2-(1H-indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-amide	561,69	95	1.81	2660	IA
81	N-{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-2-pyrrol-1-yl-benzamide	559,72	98	1.71	361	IA
82	(S)-3-(1H-Indol-3-yl)-2-[2-(4-methoxy-phenyl)-ethanoylamino]-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	538,70	98	1.71	1694	IA
83	(S)-2-[2-(4-Dimethylamino-phenyl)-ethanoylamino]-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	551,74	100	1.36	2708	IA
84	(S)-3-(1H-Indol-3-yl)-2-methyl-2-[2-(2-nitro-phenyl)-ethanoylamino]-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	553,67	95	1.5	1979	IA

| 85 | (S)-3-(1H-Indol-3-yl)-2-[2-(2-methoxy-phenyl)-ethanoylamino]-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide | 538,70 | 100 | 1.57 | 1326 | 2479 |

IA: IC50 > 10000 nM

N-acyl derivative of Intermediate III-6

Example 86

1H-Indole-2-carboxylic acid ((S)-2-(1H-indol-3-yl)-1-{[1-(5-methoxy-pyridin-2-yl)-cyclohexylmethyl]-carbamoyl}-1-methyl-ethyl)-amide

To a solution of 1-*H*-Indole-2-carboxylic acid (38 mg, 0.24 mmol), **Intermediate III-6** (100 mg, 0.19 mmol) and diisopropylethylamine (61 mg, 0.47 mmol) in DMF (5 mL) was added HBTU (90 mg, 0.24 mmol). The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated under reduced pressure and the residue was diluted with ethyl acetate, washed with brine, dried (MgSO$_4$) and concentrated under reduced pressure. The residue was purified by column chromatography (60% ethyl acetate/heptane) to give **Example 86** as an amorphous white solid (65 mg, 61%).

IR (film): 3285, 2931, 2855, 1651, 1537, 1489, 1456, 1420, 1342, 1310, 1267, 1028, 908, 744 cm^{-1};

NMR (CDCl$_3$): δ = 1.10-1.61 (11H, m), 1.95-2.04 (2H, m), 3.29-3.52 (4H, m), 3.43 (3H, s), 6.47 (1H,s), 6.86-6.90 (1H, m), 6.98-6.99 (2H, m), 7.09-7.42 (8H, m), 7.52-7.58 (2H, m), 7.73-7.74 (1H, m) 8.05 (1H, s), 9.11 (1H, s);

MS m/e (ES+): 564 (M$^+$ + H, 100%).

Binding studies of **Example 86** to the bombesin receptors gave the following results (IC$_{50}$): BB1: 11 nM, BB2: 119 nM.

Examples 87-110

N-terminal urethane derivatives of Intermediate III-7

Scheme 9 describes the synthesis of urethane derivatives of **Intermediate III-7**:

– Conversion of alcohol into 4-nitrophenyl carbonates

– *N*-terminal urethane formation

Scheme 9
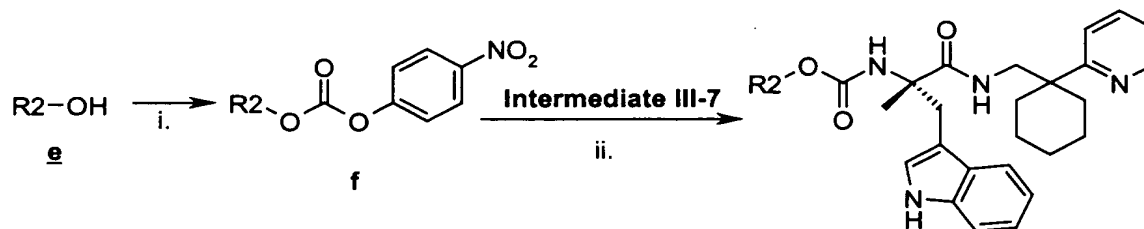
Examples 87-110

5   i.   4-nitrophenyl chloroformate, pyridine, THF

ii.   DMAP, DMF

In scheme 9, R2 represents the rest of the intermediate e. These intermediates e are listed in table 4.

10   To a stirred solution of alcohol e (10 mmol) and 4-nitrophenyl chloroformate (2.01 g, 10 mmol) in dichloromethane (50 mL) at 0°C was added dropwise a solution of pyridine (0.81 mL, 10 mmol) in dichloromethane (10 mL). The reaction mixture was allowed to slowly warm to room temperature and was stirred at room temperature for 16 h. The solvent was removed under reduced pressure and the residue was taken up in ethyl acetate (50 mL) and was washed successively with 10% citric acid (2x30 mL), water (30 mL), sat. $NaHCO_3$ 15 solution (2x50 mL) and brine (50 mL). The organic phase was dried ($MgSO_4$) and was concentrated under reduced pressure. The crude product was recrystallised from typically ethyl acetate, diethyl ether or heptane to give pure carbonate f. The product was characterised by IR (see Table 4 for carbonate signals).

20

To carbonate f (0.21 mmol) was added DMF (0.4 mL) followed by 0.50 M DMAP in DMF (400 μL, 0.20 mmol) and 0.50 M **Intermediate III-7** in DMF (200 μL, 0.10 mmol). The solution was shaken on an orbital shaker at room temperature for 42 h. Water (1.0 mL) was added and the mixture was loaded onto a LC-18 SPE cartridge (0.5 g sorbent) and the 25   cartridge was eluted with 25% methanol/water (3.4 mL) and methanol (4 mL). The methanol fraction was concentrated and purified by prep. HPLC (column: Phenomenex primesphere 10 μ C18-HC 110A, 100x21.20 mm; mobile phase: methanol/water 10 to 100% gradient). The products were characterised and analysed by LCMS (column: 50x4.6 mm Prodigy ODSIII

(5µ) column; mobile phase: acetonitrile/water (0.1% formic acid) 5 to 100% gradient over 2 min, held at 100% acetonitrile for 1 min; flow rate 4 mL/min; UV detection at 215 nm; mass spec: 150-900 Da full scan APCI+ centroid data).

5   The following products were made by the above method, with the starting material listed in Table 4 and gave the test results indicated in Table 5:

TABLE 4

Example	intermediate e	intermediate f: IR (cm⁻¹)
87	Naphthalen-1-yl-methanol	1754
88	(3,4-Dimethoxy-phenyl)-methanol	1754
89	Naphthalen-2-yl-methanol	1752
90	Indan-2-ol	1765
91	(3,4-Dichloro-phenyl)-methanol	1754
92	(4-Methoxy-phenyl)-methanol	1748
93	(4-Chloro-phenyl)-methanol	1761
94	(2-Fluoro-phenyl)-methanol	1752
95	(2-Chloro-phenyl)-methanol	1764
96	(4-Nitro-phenyl)-methanol	1761
97	o-Tolyl-methanol	1757
98	(4-tert-Butyl-phenyl)-methanol	1766
99	(3-Nitro-phenyl)-methanol	1769
100	(2-Methoxy-phenyl)-methanol	1766
101	(4-Trifluoromethyl-phenyl)-methanol	1763
102	(3-Ethoxy-phenyl)-methanol	1767
103	3-Hydroxymethyl-benzonitrile	1769
104	(2,4-Dichloro-phenyl)-methanol	1768
105	m-Tolyl-methanol	1757
106	(3-Phenoxy-phenyl)-methanol	1766
107	(3-Trifluoromethyl-phenyl)-methanol	1770

108	p-Tolyl-methanol	1759
109	(2,3-Dichloro-phenyl)-methanol	1758
110	Quinolin-6-yl-methanol	1761

TABLE 5

Example No	Product	MH$^+$	Purity %	LCMS Ret time (min)	BB1 IC50 (nm)	BB2 IC50 (nm)
87	{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid naphthalen-1-ylmethyl ester	574,73	100	1.67	239	IA
88	{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 3,4-dimethoxy-benzyl ester	584,72	95	1.41	1758	IA
89	{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid naphthalen-2-ylmethyl ester	574,73	100	1.67	1001	IA
90	{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid indan-2-yl ester	550,71	91	1.59	955	IA
91	{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 3,4-dichloro-benzyl ester	593,56	93	1.73	202	IA
92	{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 4-methoxy-benzyl ester	554,70	93	1.49	1610	IA
93	{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 4-chloro-benzyl ester	559,11	98	1.62	681	IA

5

94	{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 2-fluoro-benzyl ester	542,66	91	1.52	923	IA
95	{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 2-chloro-benzyl ester	559,11	89	1.62	624	IA
96	{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 4-nitro-benzyl ester	569,67	97	1.51	41	463
97	{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 2-methyl-benzyl ester	538,70	94	11.60	751	IA
98	{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 4-tert-butyl-benzyl ester	580,78	100	1.86	1986	IA
99	{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 3-nitro-benzyl ester	569,67	97	1.51	17	612
100	{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 2-methoxy-benzyl ester	554,70	96	1.52	818	IA
101	{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 4-trifluoromethyl-benzyl ester	592,67	97	1.7	1102	IA
102	{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 3-ethoxy-benzyl ester	568,72	89	1.60	1065	IA
103	{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 3-cyano-benzyl ester	549,68	99	1.43	85	IA

104	{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 2,4-dichloro-benzyl ester	593,56	95	1.78	450	IA
105	{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 3-methyl-benzyl ester	538,70	96	1.59	841	IA
106	{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 3-phenoxy-benzyl ester	616,77	96	1.78	1350	IA
107	{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 3-trifluoromethyl-benzyl ester	592,67	96	1.67	182	IA
108	{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 4-methyl-benzyl ester	538,70	97	1.60	1084	IA
109	{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 2,3-dichloro-benzyl ester	593,56	94	1.73	152	IA
110	{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid quinolin-6-ylmethyl ester	575,72	97	1.22	171	IA

Examples 111-168

N-terminal sulfonamide derivatives of Intermediate III-7
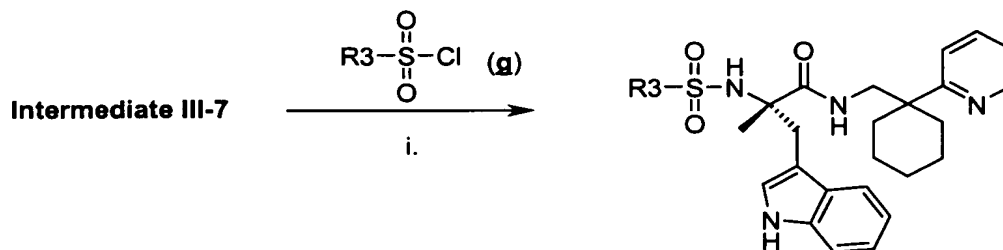
Scheme 10

Examples 111-168

In scheme 10, R3 represents the rest of the intermediate g. These intermediates g are listed in table 6.

To sulfonyl chloride **g** (0.14 mmol) was added 0.143 M **Intermediate III-7** in DMF
5 (700 µL, 0.10 mmol) followed by 300 µL of a solution containing a mixture of diisopropylethylamine (0.667 M in DMF, 0.20 mmol) and 4-dimethylaminopyridine (0.033 M in DMF, 0.01 mmol). The reaction mixture was shaken in an orbital shaker at 70°C for 16 h. The crude reaction mixture was loaded onto a 5 g silica cartridge and the cartridge was eluted with ethyl acetate in heptane (30 to 100% gradient). Removal of the solvent under
10 reduced pressure gave the sulfonamides (**Examples 111-168**). The purity of the sulfonamide was checked by LCMS. Those samples that were less than 95% pure were further purified by prep HPLC (column: YMC-Pack ODS-AM, 5µm, 150x20 mm; mobile phase: acetonitrile / water 40 to 100% gradient). The products were characterised and analysed by LCMS (column: 150x4.6 mm Prodigy ODS3 (3µ) column; mobile phase: acetonitrile (0.085% TFA)
15 / water (0.1% TFA) 20 to 100% gradient over 7 min, held at 100% acetonitrile (0.085% TFA) for 1 min; flow rate 1.5 mL/min; detection: diode array 200-300 nm; mass spec: 150-900 Da full scan APCI+ centroid data) (see Table 7).

The following examples were made by the above method, with the starting material
20 listed in Table 6 and gave the test results indicated in Table 7:

TABLE 6

Example	intermediate g
111	Phenyl-methanesulfonyl chloride
112	4-Methyl-benzenesulfonyl chloride
113	2-Chloro-benzenesulfonyl chloride
114	2-Fluoro-benzenesulfonyl chloride
115	Naphthalene-1-sulfonyl chloride
116	4-Chloro-benzenesulfonyl chloride
117	5-Dimethylamino-naphthalene-1-sulfonyl chloride
118	Naphthalene-2-sulfonyl chloride

119	Thiophene-2-sulfonyl chloride
120	Quinoline-8-sulfonyl chloride
121	3-Nitro-benzenesulfonyl chloride
122	4-Fluoro-benzenesulfonyl chloride
123	4-Nitro-benzenesulfonyl chloride
124	3-Trifluoromethyl-benzenesulfonyl chloride
125	3,4-Dichloro-benzenesulfonyl chloride
126	3-Fluoro-benzenesulfonyl chloride
127	4-Trifluoromethyl-benzenesulfonyl chloride
128	5-Chloro-thiophene-2-sulfonyl chloride
129	2-Trifluoromethyl-benzenesulfonyl chloride
130	3-Chloro-benzenesulfonyl chloride
131	3-Methyl-benzenesulfonyl chloride
132	3,4-Dimethoxy-benzenesulfonyl chloride
133	4-Cyano-benzenesulfonyl chloride
134	2-Cyano-benzenesulfonyl chloride
135	5-Chloro-1,3-dimethyl-1*H*-pyrazole-4-sulfonyl chloride
136	3,5-Dimethyl-isoxazole-4-sulfonyl chloride
137	Benzo[1,2,5]thiadiazole-4-sulfonyl chloride
138	1-Methyl-1*H*-imidazole-4-sulfonyl chloride
139	Benzo[1,2,5]oxadiazole-4-sulfonyl chloride
140	3-Chlorosulfonyl-thiophene-2-carboxylic acid methyl ester
141	5-Isoxazol-3-yl-thiophene-2-sulfonyl chloride
142	(2-Nitro-phenyl)-methanesulfonyl chloride
143	3-Cyano-benzenesulfonyl chloride
144	1,2-Dimethyl-1*H*-imidazole-4-sulfonyl chloride
145	3-Methoxy-benzenesulfonyl chloride
146	8-Nitro-naphthalene-1-sulfonyl chloride
147	2-Chloro-5-nitro-benzenesulfonyl chloride
148	2,4,6-Trichloro-benzenesulfonyl chloride
149	4-Chloro-2-nitro-benzenesulfonyl chloride
150	5-Benzenesulfonyl-thiophene-2-sulfonyl chloride
151	4-Trifluoromethoxy-benzenesulfonyl chloride

152	5-Methyl-2-phenoxy-benzenesulfonyl chloride
153	2-*p*-Tolyloxy-benzenesulfonyl chloride
154	Biphenyl-2-sulfonyl chloride
155	2-Chlorosulfonyl-benzoic acid methyl ester
156	3-Chloro-4-fluoro-benzenesulfonyl chloride
157	2,5-Dichloro-thiophene-3-sulfonyl chloride
158	3-Chloro-4-methyl-benzenesulfonyl chloride
159	2-Methoxy-4-methyl-benzenesulfonyl chloride
160	5-Pyridin-2-yl-thiophene-2-sulfonyl chloride
161	5-Bromo-6-chloro-pyridine-3-sulfonyl chloride
162	2,4-Dinitro-benzenesulfonyl chloride
163	4-Methanesulfonyl-benzenesulfonyl chloride
164	4-*tert*-Butyl-benzenesulfonyl chloride
165	2,4-Dichloro-5-methyl-benzenesulfonyl chloride
166	Chloro-trifluoromethyl-benzenesulfonyl chloride
167	Nitro-trifluoromethyl-benzenesulfonyl chloride
168	4-Butyl-benzenesulfonyl chloride

TABLE 7

Example No	Product	MH⁺	Purity %	LCMS Ret time (min)	BB1 IC50 (nm)	BB2 IC50 (nm)
111	(S)-3-(1H-Indol-3-yl)-2-methyl-2-phenylmethanesulfonylamino-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	544,72	100	4.64	186	IA
112	(S)-3-(1H-Indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-2-(toluene-4-sulfonylamino)-propionamide	544,72	100	4.74	557	IA
113	(S)-2-(2-Chloro-benzenesulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	565,14	100	4.71	257	IA

114	(S)-2-(2-Fluoro-benzenesulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	548,68	100	4.54	267	IA
115	(S)-3-(1H-Indol-3-yl)-2-methyl-2-(naphthalene-1-sulfonylamino)-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	580,76	99	4.98	185	1576
116	(S)-2-(4-Chloro-benzenesulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	565,14	97	4.89	373	4386
117	(S)-2-(5-Dimethylamino-naphthalene-1-sulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	623,82	100	4.39	1302	IA
118	(S)-3-(1H-Indol-3-yl)-2-methyl-2-(naphthalene-2-sulfonylamino)-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	580,76	100	5.01	322.	IA
119	(S)-3-(1H-Indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-2-(thiophene-2-sulfonylamino)-propionamide	536,72	99	4.39	232	Ia
120	(S)-3-(1H-Indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-2-(quinoline-8-sulfonylamino)-propionamide	581,74	99	4.53	108	IA
121	(S)-3-(1H-Indol-3-yl)-2-methyl-2-(3-nitro-benzenesulfonylamino)-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	575,69	99	4.58	208	1960
122	(S)-2-(4-Fluoro-benzenesulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	548,68	100	4.60	560	4165
123	(S)-3-(1H-Indol-3-yl)-2-methyl-2-(4-nitro-benzenesulfonylamino)-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	575,69	98	4.65	515	IA

124	(S)-3-(1H-Indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-2-(3-trifluoromethyl-benzenesulfonylamino)-propionamide	599,58	100	5.03	440	2246
125	(S)-2-(3,4-Dichloro-benzenesulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	599,58	99	5.47	216	IA
126	(S)-2-(3-Fluoro-benzenesulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	548,68	100	4.65	407	2761
127	(S)-3-(1H-Indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-2-(4-trifluoromethyl-benzenesulfonylamino)-propionamide	598,69	95	5.31	553	IA
128	(S)-2-(5-Chloro-thiophene-2-sulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	571,17	99	4.94	404	IA
129	(S)-3-(1H-Indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-2-(2-trifluoromethyl-benzenesulfonylamino)-propionamide	598,69	99	5.11	134	-
130	(S)-2-(3-Chloro-benzenesulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	565,14	99	5.05	331	2687
131	(S)-3-(1H-Indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-2-(toluene-3-sulfonylamino)-propionamide	544,72	99	4.93	393	1019
132	(S)-2-(3,4-Dimethoxy-benzenesulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	590,75	98	4.50	608	IA
133	(S)-2-(4-Cyano-benzenesulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	555,70	99	4.61	766	IA

134	(S)-2-(2-Cyano-benzenesulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	555,70	97	4.62	408	IA
135	(S)-2-(5-Chloro-1,3-dimethyl-1H-pyrazole-4-sulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	583,16	98	4.38	1252	IA
136	(S)-2-(3,5-Dimethyl-isoxazole-4-sulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	549,70	96	4.54	515	IA
137	(S)-2-(Benzo[1,2,5]thiadiazole-4-sulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	588,76	97	4.67	256	IA
138	(S)-3-(1H-Indol-3-yl)-2-methyl-2-(1-methyl-1H-imidazole-4-sulfonylamino)-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	534,69	100	3.60	3667	IA
139	(S)-2-(Benzo[1,2,5]oxadiazole-4-sulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	572,69	100	4.70	507	IA
140	3-{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethylsulfamoyl}-thiophene-2-carboxylic acid methyl ester	594,76	100	4.79	167	IA
141	(S)-3-(1H-Indol-3-yl)-2-(5-isoxazol-3-yl-thiophene-2-sulfonylamino)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	603,77	98	4.60	534	IA
142	(S)-3-(1H-Indol-3-yl)-2-methyl-2-(2-nitro-phenylmethanesulfonylamino)-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	589,72	100	4.65	430	IA
143	(S)-2-(3-Cyano-benzenesulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	555,70	99	4.55	460	IA
144	(S)-2-(1,2-Dimethyl-1H-imidazole-4-sulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	548,71	96	3.55	2482	IA

145	(S)-3-(1H-Indol-3-yl)-2-(3-methoxy-benzenesulfonylamino)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	560,72	99	4.75	295	3686
146	(S)-3-(1H-Indol-3-yl)-2-methyl-2-(8-nitro-naphthalene-1-sulfonylamino)-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	625,75	99	4.89	177	IA
147	(S)-2-(2-Chloro-5-nitro-benzenesulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	610,14	96	5.00	374	Ia
148	(S)-3-(1H-Indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-2-(2,4,6-trichloro-benzenesulfonylamino)-propionamide	634,03	100	5.45	215	Ia
149	(S)-2-(4-Chloro-2-nitro-benzenesulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	610,14	100	5.13	513	IA
150	(S)-2-(5-Benzenesulfonyl-thiophene-2-sulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	676,88	100	5.03	297	IA
151	(S)-3-(1H-Indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-2-(4-trifluoromethoxy-benzenesulfonylamino)-propion amide	614,69	99	5.35	635	IA
152	(S)-3-(1H-Indol-3-yl)-2-methyl-2-(5-methyl-2-phenoxy-benzenesulfonylamino)-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	636,82	97	5.79	76	IA
153	(S)-3-(1H-Indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-2-(2-p-tolyloxy-benzenesulfonylamino)-propionamide	636,82	97	5.79	90	IA
154	(S)-2-(Biphenyl-2-sulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	606,79	97	5.52	166	IA

155	2-{(S)-2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethylsulfamoyl}-benzoic acid methyl ester	588,73	99	4.84	242	IA
156	(S)-2-(3-Chloro-4-fluoro-benzenesulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	583,13	95	5.12	284	1216
157	(S)-2-(2,5-Dichloro-thiophene-3-sulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	605,61	99	5.23	214	IA
158	(S)-2-(3-Chloro-4-methyl-benzenesulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	579,17	97	5.28	299	3939
159	(S)-3-(1H-Indol-3-yl)-2-(2-methoxy-4-methyl-benzenesulfonylamino)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	574,75	96	4.92	445	IA
160	(S)-3-(1H-Indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-2-(5-pyridin-2-yl-thiophene-2-sulfonylamino)-propionamide	613,81	100	4.79	344	IA
161	(S)-2-(5-Bromo-6-chloro-pyridine-3-sulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	645,02	95	5.09	187	IA
162	(S)-2-(2,4-Dinitro-benzenesulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	620,69	100	4.97	475	IA
163	(S)-3-(1H-Indol-3-yl)-2-(4-methanesulfonyl-benzenesulfonylamino)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	608,78	98	4.20	1043	IA
164	(S)-2-(4-tert-Butyl-benzenesulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	586,80	96	5.65	406	IA
165	(S)-2-(2,4-Dichloro-5-methyl-benzenesulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	613,61	97	5.64	172	IA

166	(S)-2-(Chloro-trifluoromethyl-benzenesulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	633,14	100	5.33	627	IA
167	(S)-3-(1H-Indol-3-yl)-2-methyl-2-(nitro-trifluoromethyl-benzenesulfonylamino)-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	643,69	100	5.34	758	IA
168	(S)-2-(4-Butyl-benzenesulfonylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide	586,80	96	5.84	492	IA